PCT/US 04/13004

The Patent Office

INVESTOR IN PEOPLE

REC'D 12 JUL 2004
WIPO PCT

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

Signed

Dated 7 July 2003

Patents Form 1/77

Patents Act 1977
(Rule 16)

1/77

11JUN03 E814188-1 001348
P01/7700 0.00-0313463.2

THE PATENT OFFICE
M
11 JUN 2003
NEWPORT

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference

P15735-GB

2. Patent application number
(The Patent Office will fill in this part)

11 JUN 2003 0313463.2

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

ELI LILLY AND COMPANY,
LILLY CORPORATE CENTER,
INDIANAPOLIS,
INDIANA 46285, USA

Patents ADP number *(if you know it)*

428904002

If the applicant is a corporate body, give the country/state of its incorporation

STATE OF INDIANA, U.S.A.

4. Title of the invention

INHIBITORS OF MONOAMINE UPTAKE

5. Name of your agent *(if you have one)*

KINGSBURY, Oliver William

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

EUROPEAN PATENT OPERATIONS,
LILLY RESEARCH CENTRE,
ERL WOOD MANOR,
SUNNINGHILL ROAD,
WINDLESHAM,
SURREY, GU20 6PH, UK

Patents ADP number *(if you know it)*

07910276002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	122 ✓
Claim(s)	8 ✓ W-
Abstract	0
Drawing(s)	0

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature O.L.V.K-M Date 10 June 2003

12. Name and daytime telephone number of person to contact in the United Kingdom: SUAREZ-MILES, Ana 01276 483129

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *If you have answered 'Yes' Patents Form 7/77 will need to be filed.*

e) *Once you have filled in the form you must remember to sign and date it.*

f) *For details of the fee and ways to pay please contact the Patent Office.*

INHIBITORS OF MONOAMINE UPTAKE

The present invention is directed to compounds which inhibit the uptake of one or more physiologically active monoamines selected from serotonin (also called 5-hydroxytryptamine or 5-HT), norepinephrine (also called noradrenaline) and dopamine. There is a large body of scientific evidence pointing to the physiological role of these monoamines as neurotransmitters. Consequently, compounds which are capable of inhibiting the uptake of one or more of these monoamines find utility in the treatment of disorders of the central and/or peripheral nervous system.

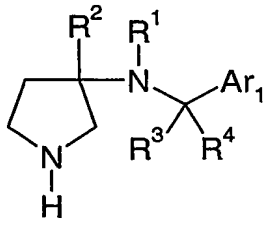
It is known that the 3-aryloxy-3-substituted-1-aminopropane class of compounds have demonstrated particular diversity in their ability to inhibit the uptake of monoamines. Fluoxetine (N-methyl 3-((4-trifluoromethylphenyl)oxy)-3-phenyl-1-aminopropane hydrochloride), for example, is a selective serotonin uptake inhibitor that has found great market acceptance in the treatment of depression and has also been approved for the treatment of a number of other disorders. Atomoxetine ((-)-N-methyl 3-((2-methylphenyl)oxy)-3-phenyl-1-aminopropane hydrochloride), is a selective norepinephrine uptake inhibitor that is approved for the treatment of attention deficit/hyperactivity disorder. Duloxetine ((+)-N-methyl 3-(1-naphthalenyloxy)-3-(2-thienyl)-1-aminopropane hydrochloride), is a dual serotonin and norepinephrine uptake inhibitor that is in clinical development for the treatment of depression.

WO 01/53258 discloses the compound 3-[(phenylmethyl)-(3S)-3-pyrrolidinylamino]-propanenitrile as an intermediate in the synthesis of nitrogenous cyclic compounds which are useful as calcium antagonists

It would be advantageous to provide further compounds which are capable of inhibiting the uptake of one or more monoamines selected from serotonin, norepinephrine and dopamine. Preferably, such compounds would exhibit one or more of the following characteristics when compared with known monoamine uptake inhibitors – (i) improved potency in their inhibition of one or more of these monoamines, (ii) improved selectivity in their inhibition of one or more of these monoamines, (iii) improved bioavailability, (iv)

minimal interaction with metabolic enzymes such as CYP2D6 and (v) improved acid stability.

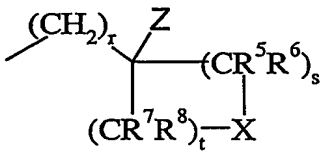
Accordingly, the present invention provides a compound of formula I



(I)

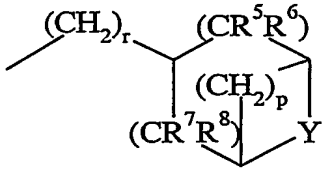
wherein

R^1 is C_1-C_6 alkyl (optionally substituted with 1, 2 or 3 halo substituents and/or with 1 substituent selected from -S-(C_1-C_3 alkyl), -O-(C_1-C_3 alkyl) (optionally substituted with 1, 2 or 3 F atoms), -O-(C_3-C_6 cycloalkyl), -SO_2-(C_1-C_3 alkyl), -CN, -COO-(C_1-C_2 alkyl) and –OH); C_2-C_6 alkenyl; -$(CH_2)_q$-Ar_2; or a group of formula (i) or (ii)



(i)

,



(ii)

;

R^2, R^3 and R^4 are each independently selected from hydrogen or C_1-C_2 alkyl;

R^5, R^6, R^7 and R^8 are at each occurrence independently selected from hydrogen or C_1-C_2 alkyl;

-X- is a bond, -CH_2-, -CH=CH-, -O-, -S-, or -SO_2-;

-Y- is a bond, -CH_2- or -O-;

-Z is hydrogen, –OH or -O-(C_1-C_3 alkyl);

p is 0, 1 or 2;

q is 0, 1 or 2;

r is 0 or 1;

s is 0, 1, 2 or 3;

t is 0, 1, 2 or 3;

Ar_1 is phenyl, pyridyl, thiazolyl, benzothiophenyl or naphthyl; wherein said phenyl, pyridyl or thiazolyl group may be substituted with 1, 2 or 3 substituents each independently selected from halo, cyano, C_1-C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1-C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms) and -S-(C_1-C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms) and/or with 1 substituent selected from pyridyl, pyrazole, phenyl (optionally substituted with 1, 2 or 3 halo substituents) and phenoxy (optionally substituted with 1, 2 or 3 halo substituents); and wherein said benzothiophenyl or naphthyl group may be optionally substituted with 1, 2 or 3 substituents each independently selected from halo, cyano, C_1-C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1-C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms), and -S-(C_1-C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms);

Ar_2 is naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl, wherein said naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl may be substituted with 1, 2 or 3 substituents each independently selected from halo, C_1-C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms) and -O-(C_1-C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms); and pharmaceutically acceptable salts thereof;

provided that

(a) the cyclic portion of the group of formula (i) must contain at least three carbon atoms and not more than seven ring atoms;

(b) when –X- is –CH=CH-, then the cyclic portion of the group of formula (i) must contain at least five carbon atoms; and

(c) when –Z is –OH or -O-(C_1-C_3 alkyl), then –X- is -CH_2-;

(d) when –Y- is –O- then p cannot be 0; and

(e) the compound 3-[(phenylmethyl)-(3S)-3-pyrrolidinylamino]-propanenitrile is excluded.

In the present specification the term "C_1-C_6 alkyl" means a monovalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having from 1 to 6 carbon atoms.

In the present specification the term "C_2-C_6 alkenyl" means a monovalent unsubstituted unsaturated straight-chain or branched-chain hydrocarbon radical having from 2 to 6 carbon atoms and containing at least one carbon-carbon double bond.

In the present specification the term "C_3-C_6 cycloalkyl" means a monovalent unsubstituted saturated cyclic hydrocarbon radical having from 3 to 6 carbon atoms.

In the present specification the term "C_1-C_6 alkylene" means a divalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having from 1 to 6 carbon atoms.

In the present specification the term "halo" or "halogen" means F, Cl, Br or I.

In the present specification the term "C_1-C_4 difluoroalkyl" means a monovalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having from 1 to 4 carbon atoms wherein two hydrogen atoms are substituted with two fluoro atoms. Preferably the two fluoro atoms are attached to the same carbon atom.

In the present specification the term "C_1-C_4 trifluoroalkyl" means a monovalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having from 1 to 4 carbon atoms wherein three hydrogen atoms are substituted with three fluoro atoms. Preferably the three fluoro atoms are attached to the same carbon atom.

In the present specification the term "phenoxy" means a monovalent unsubstituted phenyl radical linked to the point of substitution by an O atom.

In the present specification the term "pyridyl" includes 2-pyridyl, 3-pyridyl and 4-pyridyl.

In the present specification the term "furyl" includes 2-furyl and 3-furyl. 2-furyl is preferred.

In the present specification the term "thiophenyl" includes 2-thiophenyl and 3-thiophenyl.

In the present specification the term "thiazolyl" includes 2-thiazolyl, 4-thiazolyl and 5-thiazolyl.

In the present specification the term "pyrazole" includes 1-pyrazole, 3-pyrazole and 4-pyrazole. 1-pyrazole is preferred.

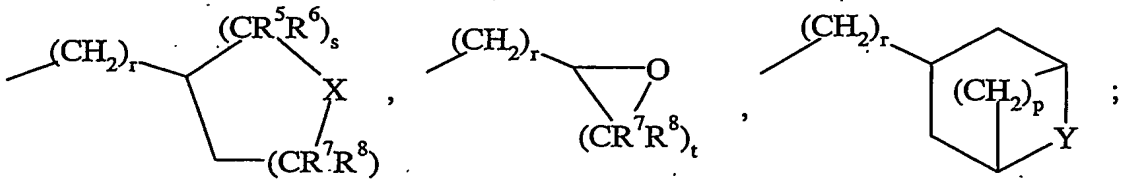
In the present specification the term "benzothiophenyl" includes 2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl and 7-benzo[b]thiophenyl.

In the present specification the term "naphthyl" includes 1-naphthyl, and 2-naphthyl. 1-naphthyl is preferred.

In the above definitions, similar terms specifying different numbers of C atoms take an analogous meaning. For example the terms "C_1-C_4 alkyl" and "C_1-C_3 alkyl" mean a monovalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having from 1 to 4 and 1 to 3 carbon atoms respectively. The term "C_1-C_4 alkyl" includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and tert-butyl. The term "C_1-C_3 alkyl" includes methyl, ethyl, n-propyl and iso-propyl.

It will be appreciated that when s is 2 or 3, then each R^5 and/or each R^6 can be different. In the same way when t is 2 or 3, then each R^7 and/or each R^8 can be different.

In a preferred embodiment of the present invention R^1 is C_1-C_6 alkyl, C_2-C_6 alkenyl, -$(CH_2)_m$-CF_3, -$(CH_2)_n$-S-(C_1-C_3 alkyl), -CH_2-COO-(C_1-C_2 alkyl), -(C_1-C_5 alkylene)-O-(C_1-C_3 alkyl), -(C_1-C_5 alkylene)-O-(C_3-C_6 cycloalkyl), -(C_1-C_5 alkylene)-SO_2-(C_1-C_3 alkyl), -(C_1-C_5 alkylene)-OCF_3, -(C_1-C_6 alkylene)-OH, -(C_1-C_5 alkylene)-CN, -$(CH_2)_q$-Ar_2 or a group of formula (ia), (ib) or (ii)



(ia) (ib) (ii)

R^2, R^3, R^4, R^5, R^6, R^7, R^8, -X-, -Y-, p, q, r and s have the values defined above;

m is 1, 2 or 3;

n is 1, 2 or 3;

t is 2, 3 or 4;

-Ar_1 is phenyl, pyridyl, thiazolyl or naphthyl; wherein said phenyl, pyridyl or thiazolyl group may be substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl, cyano, C_1-C_4 alkyl, -O-(C_1-C_4 alkyl), -O-(C_1-C_4 difluoroalkyl), -O-(C_1-C_4 trifluoroalkyl), -S-(C_1-C_4 alkyl), -S-(C_1-C_2 trifluoroalkyl) and/or with 1 substituent selected from pyridyl, pyrazole, phenyl (optionally substituted with 1, 2 or 3 halo substituents) and phenoxy (optionally substituted with 1, 2 or 3 halo substituents); and wherein said naphthyl group may be optionally substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl, cyano, C_1-C_4 alkyl, -O-(C_1-C_4 alkyl), -O-(C_1-C_4 difluoroalkyl), -O-(C_1-C_4 trifluoroalkyl), -S-(C_1-C_4 alkyl), -S-(C_1-C_2 trifluoroalkyl);

Ar_2 is naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl, wherein said naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl may be substituted with 1, 2 or 3 substituents each independently selected from halo, C_1-C_4 alkyl, trifluoromethyl and -O-(C_1-C_4 alkyl);

and pharmaceutically acceptable salts thereof.

In a preferred embodiment of the present invention R^2 is hydrogen. In another preferred embodiment of the present invention R^3 and R^4 are hydrogen. More preferably R^2, R^3 and R^4 are hydrogen.

In a preferred embodiment of the present invention each R^5 and R^6 is hydrogen. In another preferred embodiment of the present invention each R^7 and R^8 is hydrogen. More

preferably R^5, R^6, R^7 and R^8 are hydrogen.

In a preferred embodiment of the present invention R^1 is C_1-C_6 alkyl. More preferably R^1 is n-propyl, 1-methylethyl, 2-methylpropyl, 3,3-dimethylpropyl.

In another preferred embodiment of the present invention R^1 is -(C_4-C_5 alkylene)-OH. More preferably R^1 is 2,2-dimethyl-2-hydroxyethyl or 3,3-dimethyl-3-hydroxypropyl.

In another preferred embodiment of the present invention R^1 is a group of formula (i) and each R^5 and R^6 is hydrogen. More preferably each R^5, R^6, R^7 and R^8 is hydrogen.

In another preferred embodiment of the present invention R^1 is a group of formula (ii) and each R^5 and R^6 is hydrogen. More preferably each R^5, R^6, R^7 and R^8 is hydrogen.

In another preferred embodiment of the present invention R^1 is a group of formula (i), r is 0, s is 2, t is 2, –Z is hydrogen and -X- is -O-, –S- or –SO_2-. More preferably R^1 is a group of formula (i), r is 0, s is 2, t is 1 or 2, –Z is hydrogen and -X- is –O-.

In another preferred embodiment of the present invention R^1 is a group of formula (i), r is 0, s is 1, 2 or 3, t is 1, –Z is hydrogen and -X- is –CH_2-.

In another preferred embodiment of the present invention R^1 is a group of formula (i), r is 1, s is 0, 1, 2 or 3, t is 1, –Z is hydrogen and -X- is –CH_2-.

In another preferred embodiment of the present invention R^1 is a group of the formula (ia). More preferably R^1 is a group of the formula (ia) and each R^5, R^6, $R^7$and R^8 is hydrogen.

In another preferred embodiment of the present invention R^1 is a group of the formula (ib). More preferably R^1 is a group of the formula (ib), r is 1, t is 3, and each $R^7$and R^8 is hydrogen.

In another preferred embodiment of the present invention R^1 is $-(CH_2)_m-CF_3$. More preferably R^1 is $-(CH_2)_m-CF_3$ and m is 1, 2, or 3.

In another preferred embodiment of the present invention R^1 is $-(CH_2)_n-S-(C_1-C_3$ alkyl). More preferably R^1 is $-(CH_2)_3-S-CH_3$.

In another preferred embodiment of the present invention R^1 is $-CH_2-COO-(C_1-C_2$ alkyl). More preferably R^1 is $-CH_2-COOCH_3$.

In another preferred embodiment of the present invention R^1 is $-(C_1-C_5$ alkylene)-O-(C_1-C_3 alkyl). More preferably R^1 is $-(C_3-C_4$ alkylene)-OCH_3.

In another preferred embodiment of the present invention R^1 is $-(C_1-C_5$ alkylene)-O-(C_3-C_6 cycloalkyl). More preferably R^1 is $-CH_2-CH_2-O$-cyclobutyl.

In another preferred embodiment of the present invention R^1 is $-(C_1-C_5$ alkylene)-$SO_2-(C_1-C_3$ alkyl).

In another preferred embodiment of the present invention R^1 is $-(C_1-C_5$ alkylene)-OCF_3. More preferably R^1 is $-CH_2-CH_2-OCF_3$.

In another preferred embodiment of the present invention R^1 is $-(C_1-C_5$ alkylene)-CN. More preferably R^1 is $-(C_2-C_4$ alkylene)-CN. Most preferably $-CH_2-CH_2-CN$ or $-CH_2-C(CH_3)_2-CN$.

In another preferred embodiment of the present invention R^1 is $-(CH_2)_q-Ar_2$, and q is 1. More preferably R^1 is $-(CH_2)_q-Ar_2$, q is 1 and $-Ar_2$ is pyridyl, phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl or C_1-C_4 alkyl.

In another preferred embodiment of the present invention $-Ar_1$ is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo,

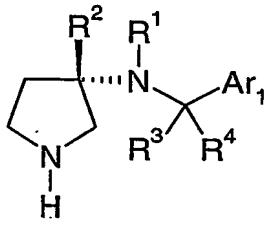
trifluoromethyl and C_1-C_4 alkyl and/or with 1 substituent selected from phenyl, phenyl substituted with 1, 2 or 3 halo substituents, pyridyl, pyrazole, phenoxy and phenoxy substituted with 1, 2 or 3 halo substituents; pyridyl; or pyridyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl and C_1-C_4 alkyl and/or with 1 substituent selected from phenyl and phenyl substituted with 1, 2 or 3 halo substituents. More preferably $-Ar_1$ is phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl and C_1-C_4 alkyl and/or with 1 substituent selected from phenyl, phenyl substituted with 1, 2 or 3 halo substituents, pyridyl, pyrazole, phenoxy and phenoxy substituted with 1, 2 or 3 halo substituents. Most preferably $-Ar_1$ is phenyl substituted with 1 or 2 substituents each independently selected from halo, trifluoromethyl and C_1-C_4 alkyl and/or with 1 substituent selected from phenyl, phenyl substituted with 1, 2 or 3 halo substituents, pyridyl, pyrazole, phenoxy and phenoxy substituted with 1, 2 or 3 halo substituents. Suitable $-Ar_1$ groups include, for example, 2-methylthiophenyl, 2-methylphenyl, 2-fluorophenyl, 2-chlorophenyl, 2-isopropoxyphenyl, 2-trifluoromethylphenyl, 2-difluoromethoxyphenyl, 2-methoxyphenyl, 2-ethoxyphenyl, 2-(1,1'-biphenyl), 2-phenoxyphenyl, 2-benzylphenyl, 3-trifluoromethoxyphenyl, 3-chlorophenyl, 3-trifluoromethylphenyl, 3-methylphenyl, 3-trifluorothiomethoxyphenyl, 3-methoxyphenyl, 4- trifluoromethylphenyl, 4-chlorophenyl, 4-fluorophenyl, 3,5-dichlorophenyl, 3,5-dimethylphenyl, 3-trifluoromethyl-5-fluorophenyl, 3,5-difluorophenyl, 2,3-dichlorophenyl, 2,3-dimethylphenyl, 2-chloro-3-trifluoromethylphenyl, 2-chloro-3-methylphenyl, 2-methyl-3-chlorophenyl, 2,4-dichlorophenyl, 2,4-dimethyl, 2,4-difluorophenyl, 2-chloro-4-fluorophenyl, 2-trifluoromethyl-4-fluorophenyl, 2-fluoro-4-trifluoromethylphenyl, 2-methyl-4-chlorophenyl, 2-methoxy-4-fluorophenyl, 2-trifluoromethyl-5-fluorophenyl, 2,5-dimethylphenyl, 4-fluoro-[1,1'-biphenyl]-2-yl, 2-chloro-5-fluorophenyl, 2-(trifluoromethyl)-6-fluorophenyl, 2-chloro-6-fluorophenyl, 3,4-dichlorophenyl, and 3-chloro-4-fluorophenyl. In general when $-Ar_1$ is phenyl substituted with pyridyl, 3-pyridyl is preferred.

In another preferred embodiment of the present invention $-Ar_1$ is pyridyl or pyridyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl and C_1-C_4 alkyl and/or with 1 substituent selected from phenyl and phenyl

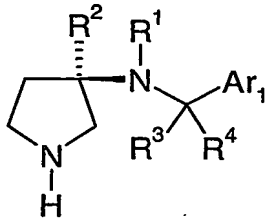
substituted with 1, 2 or 3 halo substituents. More preferably $-Ar_1$ is pyridyl substituted with 1 or 2 substituents each independently selected from halo, trifluoromethyl and C_1-C_4 alkyl and/or with 1 substituent selected from phenyl and phenyl substituted with 1, 2 or 3 halo substituents. Suitable $-Ar_1$ groups include, for example, 3-phenyl-2-pyridyl. In general when $-Ar_1$ is a substituted pyridyl, substituted 2-pyridyl is preferred.

The present invention includes pharmaceutically acceptable salts of the compounds of formula I. Suitable salts include acid addition salts, including salts formed with inorganic acids (for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acid) or with organic acids, such as organic carboxylic acids (for example fumaric, pyruvic, lactobionic, glycolic, oxalic, maleic, hydroxymaleic, malic, citric, salicylic, o-acetoxybenzoic or tartaric acid), or organic sulphonic acids (for example toluene-p-sulphonic, bisethanesulphonic or methanesulphonic acid).

It will be appreciated that certain compounds of formula I may possess one or more chiral centres. Where a structural formula does not specify the stereochemistry at one or more chiral centres, it encompasses all possible stereoisomers and all possible mixtures of stereoisomers (including, but not limited to, racemic mixtures), which may result from stereoisomerism at each of the one or more chiral centers. For example, the carbon atom at the three position of the pyrrolidine ring can give rise to two enantiomers of formulae (Ia) and (Ib):



(Ia)



(Ib)

wherein R^1, R^2, R^3, R^4 and Ar_1 have the values defined in formula (I) above, with the proviso's therein. Said isomers are also an aspect of the present invention. Preferred compounds of the invention are those of formula (Ia).

The preferred stereochemistry detailed above applies also to the compounds used as intermediates for the preparation of the compounds of the present invention.

As mentioned above, the compounds of the present invention and their pharmaceutically acceptable salts inhibit the uptake of one or more of the monoamine neurotransmitters serotonin, dopamine and norepinephrine.

In view of these properties, the compounds of the present invention and their pharmaceutically acceptable salts are indicated for use in treating disorders which are caused by or linked to decreased neurotransmission of one or more of these monoamines. Such disorders include disorders of the central and/or peripheral nervous system such as, for example, adjustment disorders (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood), age-associated learning and mental disorders (including Alzheimer's disease), alcohol addiction, antinociceptive pain, anxiety, apathy, attention-deficit (or other cognitive) disorders due to general medical conditions, attention-deficit hyperactivity disorder (ADHD), autism, bipolar disorder, borderline personality disorder, brain trauma, cardiovascular disorders, chronic fatigue syndrome, chronic or acute stress, chron's disease, cognitive disorders including mild cognitive impairment (MCI), conduct disorder, cyclothymic disorder, dementia of ageing, dementia of the Alzheimers type (DAT), depression (including adolescent depression and minor depression), dyspepsia, disruptive behavior disorders, drug addiction including cocaine abuse, dysthymic disorder, eating disorders (including bulimia and anorexia nervosa), emesis, emotional dysregulation, epilepsy, fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS), functional bowel disorders, gastric motility disorders, gastroesophageal reflux for functional bowel disorders, gastrointestinal disorders, generalized anxiety disorder (GAD), headache, hypertension, hypotensive states including orthostatic hypotension, iletis, impulsive control disorders, incontinence (i.e., stress incontinence, genuine stress incontinence, urge incontinence and mixed incontinence), inflammatory bowel disorders, inhalation disorders, insterstitial cystitis, intoxication disorders (alcohol addiction),

irritable bowel syndrome, ischemic bowel disease, mania, memory loss, mutism, nicotine addiction, obesity (i.e., reducing the weight of obese or overweight patients), obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, pain (including chronic pain, inflammatory pain, neuropathic pain, non-neuropathic non-inflammatory pain, persistent pain, persistent pain of inflammatory and/or neuropathic origin, headache and migraine), panic disorders, Parkinsonism, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder (i.e., premenstrual syndrome and late luteal phase dysphoric disorder), psoriasis, psychoactive substance use disorders, psychotic disorders (including schizophrenia, schizoaffective and schizophreniform disorders), seasonal affective disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome (i.e., wherein a patient who fails to maintain a satisfactory response to SSRI therapy after an initial period of satisfactory response), senile dementia, sexual dysfunction (including premature ejaculation and erectile difficulty), sleep disorders (such as narcolepsy and enuresis), smoking cessation, social phobia (including social anxiety disorder), specific developmental disorders, substance abuse (including alcohol addiction, tobacco abuse, symptoms caused by withdrawal or partial withdrawal from the use of tobacco or nicotine and drug addiction including cocaine abuse), TIC disorders (e.g., Tourette's Disease), tobacco addiction, trichotilomania, ulcerative colitis, urethral syndrome, vascular dementia and cognitive impairment associated with schizophrenia (CIAS).

One preferred group of compounds of the present invention selectively inhibit the reuptake of serotonin and norepinephrine over dopamine transporter. Preferably said group of compounds of the present invention selectively inhibit the reuptake of serotonin and norepinephrine relative to the dopamine transporter by a factor of at least five, and even more preferably by a factor of at least ten. Compounds of the present invention with this pharmacological profile are particularly useful for the treatment of depression, eating disorders (including bulimia and anorexia nervosa), inflammatory bowel disorders, functional bowel disorders, dyspepsia, chron's disease, iletis, ischemic bowel disease, ulcerative colitis, gastroesophageal reflux for functional bowel disorders, irritable bowel syndrome, obesity, insterstitial cystitis, urethral syndrome, gastric motility disorders, substance abuse (including alcoholism, tobacco abuse, symptoms caused by withdrawal

or partial withdrawal from the use of tobacco or nicotine and drug addiction including cocaine abuse), pain (including inflammatory pain, neuropathic pain, non-neuropathic non-inflammatory pain, persistent pain, persistent pain of inflammatory and/or neuropathic origin, headache and migraine), incontinence (including stress urinary incontinence and urge incontinence), dementia of ageing, senile dementia, Alzheimer's, memory loss, Parkinsonism, attention-deficit disorder (including attention-deficit hyperactivity disorder), anxiety, social phobia, disruptive behavior disorders, impulsive control disorders, borderline personality disorder, chronic fatigue syndrome, panic disorders, obsessive compulsive disorder, post-traumatic stress disorder, schizophrenia, gastrointestinal disorders, cardiovascular disorders, emesis, sleep disorders, cognitive disorders, psychotic disorders, brain trauma, premenstrual syndrome or late luteal syndrome, sexual dysfunction (including premature ejaculation and erectile difficulty), autism, mutism and trichotilomania. They are more particularly useful for the treatment of depression, incontinence (particularly stress urinary incontinence) and pain (particularly persistent pain). They are most particularly useful for the treatment of persistent pain.

For clinical purposes, pain may be divided into two categories: acute pain and persistent pain. Acute pain is provoked by noxious stimulation produced by injury and/or disease of skin, deep somatic structures or viscera, or abnormal function of muscle or viscera that does not produce actual tissue damage. On the other hand, persistent pain can be defined as pain that persists beyond the usual course of an acute disease or a reasonable time for an injury to heal or that is associated with a chronic pathologic process that causes continuous pain or the pain recurs at intervals for months or years. If pain is still present after a cure should have been achieved, it is considered persistent pain. For the purpose of the present invention, persistent pain can be chronic non-remitting or recurrent. The difference in definition between acute and persistent pain is not merely semantic but has an important clinical relevance. For example, a simple fracture of the wrist usually remains painful for a week to 10 days. If the pain is still present beyond the typical course of treatment, it is likely that the patient is developing reflex sympathetic dystrophy, a persistent pain syndrome that requires immediate effective therapy. Early and effective intervention potentially prevents the undue disability and suffering, and avoids the potential development of a condition that becomes refractory to therapy.

Acute and persitant pain differ in etiology, mechanisms, pathophysiology, symptomatology, diagnosis, therapy, and physiological responses. In contrast to the transitory nature of acute pain, persistent pain is caused by chronic pathologic processes in somatic structures or viscera, by prolonged and sometimes permanent dysfunction of the peripheral or central nervous system, or both. Also, persistent pain can sometimes be attributed to psychologic mechanisms and/or environmental factors.

More specifically, persistent pain can be segmented into neuropathic pain (e.g. diabetic neuropathy, infectious neuropathic pain associated with AIDS, non-surgical carpal tunnel syndromes, post-herpetic neuralgia, cervical, thoracic and lumbosacral radiculopathies, stroke-related central pains, trigeminal neuralgia and complex regional pain syndromes I and II), inflammatory pain (e.g. polymyalgia, rheumatoid arthritis and osteoarthritis), and non-neuropathic non-inflammatory pain, non-neuropathic non-inflammatory chronic pain (NNNICP) (e.g. chronic fatigue syndrome, chronic back pain without radiculopathy, fibromyalgia, chronic tension type headaches, inflammatory bowel disorders, irritable bowel syndrome, whiplash injuries, chronic pelvic pain, TMJD and failed back).

Current therapies for persistent pain include opiates, barbiturate-like drugs such as thiopental sodium and surgical procedures such as neurectomy, rhizotomy, cordotomy, and cordectomy.

Another preferred group of compounds of the present invention selectively inhibit the reuptake of norepinephrine transporter over serotonin and dopamine transporter. Preferably said group of compounds of the present invention selectively inhibit the reuptake of norepinephrine transporter relative to the serotonin and dopamine transporter by a factor of at least five, and even more preferably by a factor of at least ten. Compounds of the present invention with this pharmacological profile are particularly useful for the treatment of adjustment disorders (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood), age-associated learning and mental disorders (including Alzheimer's disease), alcohol addiction, anorexia nervosa, antinociceptive pain, apathy, attention-

deficit (or other cognitive) disorders due to general medical conditions, attention-deficit hyperactivity disorder (ADHD), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, cognitive disorders including mild cognitive impairment (MCI), conduct disorder, cyclothymic disorder, dementia of the Alzheimers type (DAT), depression (including adolescent depression and minor depression), dysthymic disorder, emotional dysregulation, fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS), generalized anxiety disorder (GAD), hypotensive states including orthostatic hypotension, incontinence (i.e., stress incontinence, genuine stress incontinence, and mixed incontinence), inhalation disorders, intoxication disorders (alcohol addiction), mania, migraine headaches, neuropathic pain, nicotine addiction, obesity (i.e., reducing the weight of obese or overweight patients), obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, pain including chronic pain, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder (i.e., premenstrual syndrome and late luteal phase dysphoric disorder), psoriasis, psychoactive substance use disorders, psychotic disorders (including schizophrenia, schizoaffective and schizophreniform disorders), seasonal affective disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome (i.e., wherein a patient who fails to maintain a satisfactory response to SSRI therapy after an initial period of satisfactory response), sleep disorders (such as narcolepsy and enuresis), social phobia (including social anxiety disorder), somatoform disorders, specific developmental disorders, TIC disorders (e.g., Tourette's Disease), tobacco addiction, vascular dementia and cognitive impairment associated with schizophrenia (CIAS). They are most particularly useful for the treatment of ADHD and schizophrenia.

Another preferred group of compounds of the present invention selectively inhibit the reuptake of norepinephrine, serotonin and dopamine transporter. Compounds of the present invention with this pharmacological profile are particularly useful for the treatment of a variety of conditions such as depression, obesity, compulsive disorders (including bulimia, obsessive compulsive disorder, drug addiction including cocaine abuse and alcohol addiction), hypertension, senile dementia, Alzheimer's, memory loss,

attention-deficit hyperactivity disorder (ADHD), sexual dysfunction, Parkinsonism, anxiety, chronic fatigue syndrome, panic disorders, cognitive disorders, schizophrenia, gastrointestinal disorders, headache, cardiovascular disorders, epilepsy, smoking cessation, pain including chronic pain, urinary incontinence, emesis and sleep disorders. They are most particularly useful for the treatment of depression, chronic pain, smoking cessation and obesity.

Accordingly, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof for use in therapy. In particular, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof for use as an inhibitor of the uptake of one or more of the monoamine neurotransmitters serotonin, dopamine and norepinephrine.

In another embodiment, the present invention provides a method for inhibiting the uptake of one or more monoamines selected from serotonin, dopamine and norepinephrine in a mammal, comprising administering to a mammal in need of such inhibition an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof. In particular, the present invention provides a method for treating a disorder which is caused by or linked to decreased neurotransmission of one or more monoamines selected from serotonin, dopamine and norepinephrine in a mammal, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof. Such disorders include, for example, disorders of the central and/or peripheral nervous system.

In the context of the present specification the terms "treating" and "treatment" include prophylactic treatment as well as curative treatment.

In another alternative embodiment, the present invention provides for the use of a compound of Formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting the uptake of one or more monoamines selected from serotonin, dopamine and norepinephrine. In particular, the present invention provides for the use of a compound of Formula I or a pharmaceutically acceptable salt thereof for the

manufacture of a medicament for the treatment of a disorder which is caused by or linked to decreased neurotransmission of one or more monoamines selected from serotonin, dopamine and norepinephrine. Such disorders include, for example, disorders of the central and/or peripheral nervous system.

The compounds may be administered by various routes and are usually employed in the form of a pharmaceutical composition.

Accordingly, in a further embodiment, the present invention provides a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier.

Such compositions may be prepared by methods well known in the pharmaceutical art and normally comprise at least one active compound in association with a pharmaceutically acceptable diluent or carrier. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier or diluted by a carrier, and/or enclosed within a carrier which may, for example, be in the form of a capsule, sachet, paper or other container.

The compositions indicated can be sterilized and/or can contain auxiliaries such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colourants, flavourings and/or one or more further active compounds. Compositions of the invention may be formulated so as to provide, quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

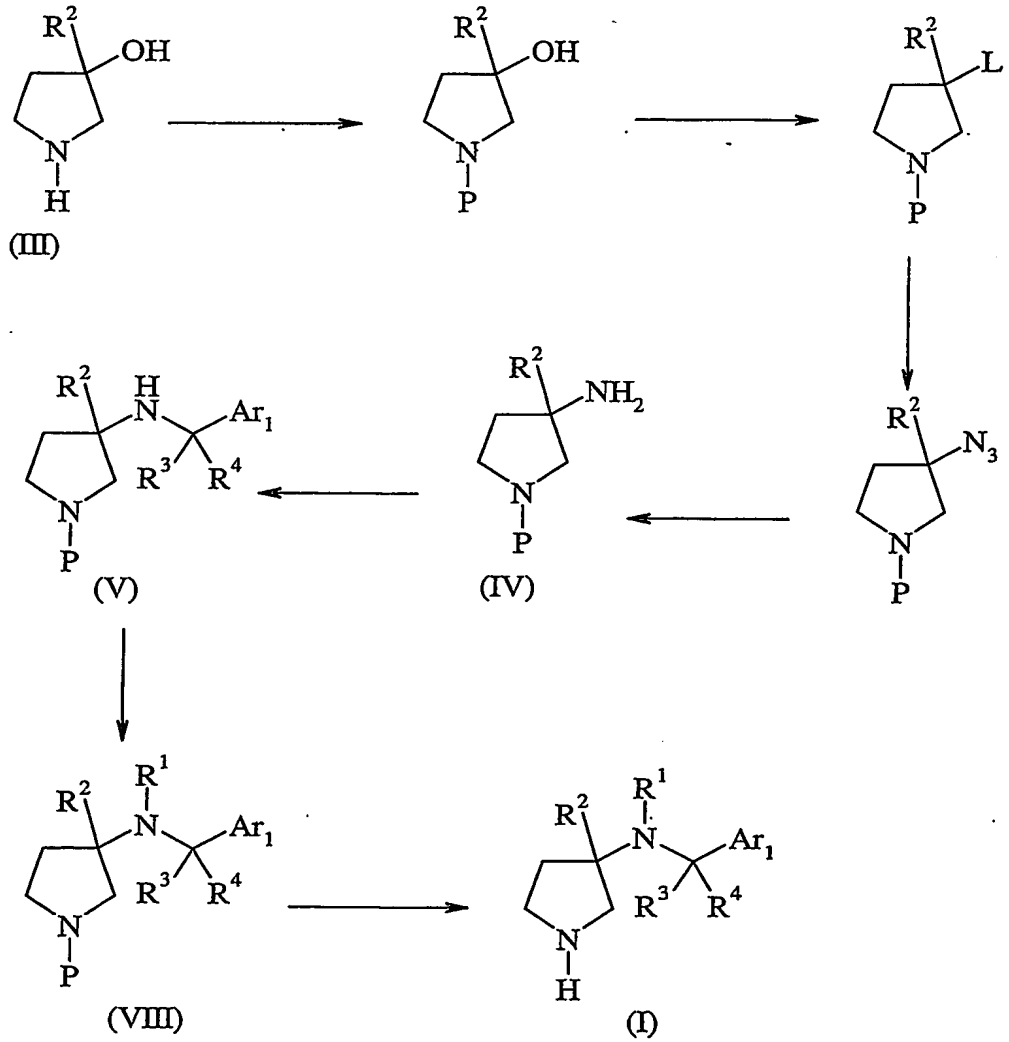
The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 500 mg of the active ingredient.

In the context of the present specification, the term "unit dosage form" refers to physically discrete units suitable as unitary doses for human subjects and other mammals, each unit containing a predetermined quantity of one or more compounds of Formula I or

pharmaceutically acceptable salts thereof, calculated to produce the desired therapeutic effect, together with a pharmaceutically acceptable diluent or carrier.

Compounds of formula I may be prepared by conventional organic chemistry techniques and also by solid phase synthesis.

Compounds of formula I can be prepared via the 3-aminopyrrolidine intermediate of formula (IV) as illustrated in the scheme 1 below:



Scheme 1

Commercially available 3-hydroxypyrrolidine of formula (III) wherein R^2 is hydrogen, can be protected using a suitable nitrogen-protecting group such as those described in

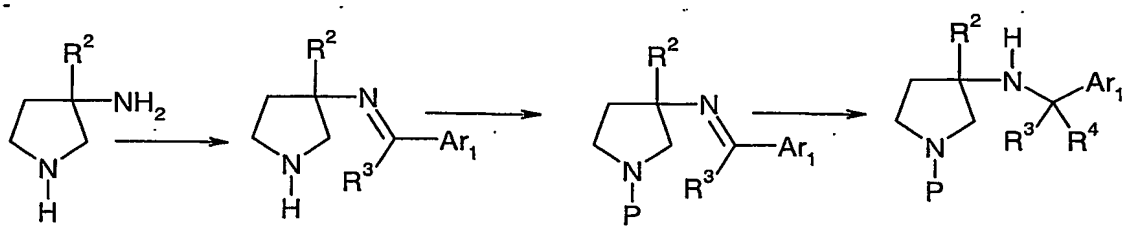
T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1991, hereafter referred to as "Greene". For example 3-*R*-hydroxypyrrolidine (III) can be protected with a tert-butoxycarbonyl group, (boc). The protection reaction can be carried out for example using Boc anhydride in a suitable solvent such as for example tetrahydrofuran (THF) or dichloromethane (DCM) in the presence of a base such as tryethylamine (TEA) or 4-(dimethylamino)pyridine (DMAP). It will be appreciated that for compounds of formula (I) wherein R^2 is C_1-C_2 alkyl, the 3-hydroxypyrrolidine of formula (III) can be prepared from the readily available 3-pyrrolidinone via addition of the appropriate C_1-C_2 alkyl organometallic.

The hydroxy group of the N-protected-3-hydroxypyrrolidine can be converted into a suitable leaving group (L) such as for example chloride, bromide, iodide or mesylate. For example the N-protected-hydroxypyrrolidine can be converted to the mesylate in the presence of mesyl chloride and a suitable base such as triethylamine in a solvent such as DCM. Said mesylate is subsequently displaced with the corresponding azide in a suitable solvent such as dimethylformamide (DMF) or dimethylsulphoxide (DMSO). This azide intermediate can be converted to the corresponding N-protected-aminopyrrolidine of formula (IV) via hydrogenation in the presence of a suitable catalyst such as Palladium on charcoal and in a suitable solvent such as methanol or ethanol.

For compounds of formula (I) wherein R^4 is H, intermediate (IV) can be alkylated via reductive alkylation with a ketone of formula R^3-CO-Ar_1 wherein R^3 and Ar_1 have the values for formula (I) above. The reductive alkylation can be carried out for example as a hydrogenation reaction in the presence of a suitable catalyst such as Palladium on charcoal and a suitable solvent such as for example ethanol. Alternatively, said reductive alkylation can be carried out in the presence of a suitable borane such as sodium triacetoxyborohydride, $NaBH(OAc)_3$ and optionally in the presence of a suitable acid such as acetic acid, in a suitable solvent such as for example dichoroethane (DCE).

Alternatively, intermediate of formula (V) wherein R^4 is H can be prepared as shown in scheme 2 below by reductive alkylation of readily available 3-aminopyrrolidine of formula (VI) wherein R^2 has the values defined for formula (I) above, followed by the

protection of the nitrogen in the pyrrolidine ring using a suitable protecting group such as those defined in Greene.

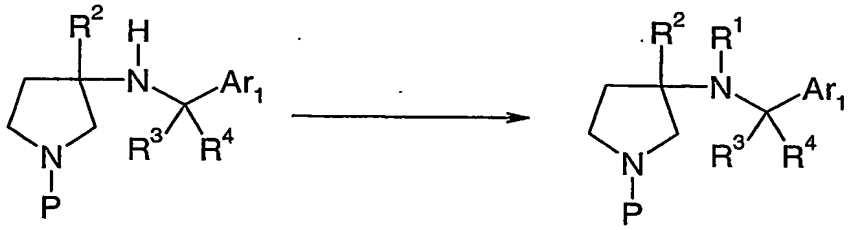


(VI) (VII) (V)

Scheme 2

For example the reductive alkylation can be carried out in the presence of a ketone of formula Ar_1-CO-R^3 wherein Ar_1 and R^3 have the values defined for formula (I) above. Initial condensation of the amino pyrrolidine with the ketone is undertaken in the presence of a suitable acid such as p-toluenesulphonic acid, in a suitable solvent such as toluene. The resultant imino pyrrolidine intermediate can then be protected with for example a boc group. The reaction can be carried out in the presence of boc anhydride and a suitable base such as DMAP, in a suitable solvent such as DCM. Said imine is reduced via hydrogenation in the presence of a suitable catalyst such as palladium on charcoal, in a suitable solvent such as ethanol to give the corresponding amine of formula (V).

Intermediate of formula (V) can be converted to compounds of formula (VIII) via reductive alkylation with an aldehyde of formula R^9-CHO, wherein R^9 is chosen such that R^9-CH_2 = R^1 and R^1 has the values defined for formula (I) above. The reductive alkylation can be carried out using standard methods, for instance as those mentioned above with the ketone Ar_1-CO-R^3.

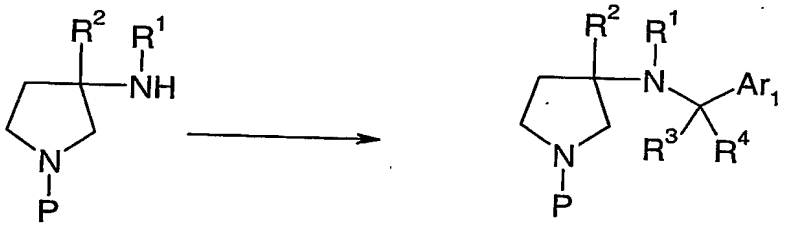


(V) (VIII)

Scheme 3

For example a compound of formula (V) can be alkylated with R^9-CHO in the presence of a suitable borane, such as $NaBH(OAc)_3$, optionally in the presence of an acid such as acetic acid, in the presence of a suitable solvent such as dichloroethane (DCE).

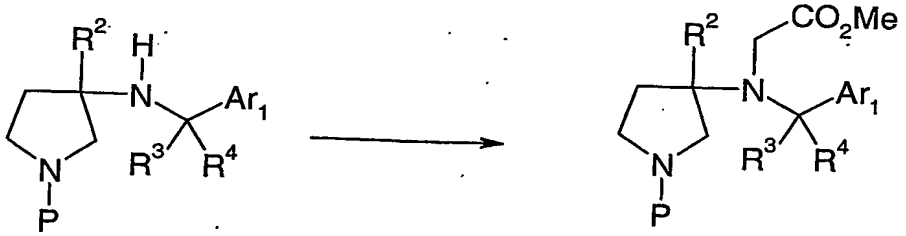
For compounds of formula (I) wherein R^3 and R^4 are hydrogen the alkylation of intermediate (V) can be carried out with a compound of formula $Ar_1CH_2L_1$ wherein L_1 is a suitable leaving group such as chloro, bromo, iodo or mesylate, in the presence of a suitable base such as potassium carbonate and a suitable solvent such as acetonitrile, to give the corresponding intermediate of formula $(VIII)_a$. It will be appreciated that the same reaction can be carried out using Ar_1-CR^3R^4-L_1 wherein R^3 and R^4 are C_1-C_2 alkyl.



(V) $(VIII)_a$

Scheme 4

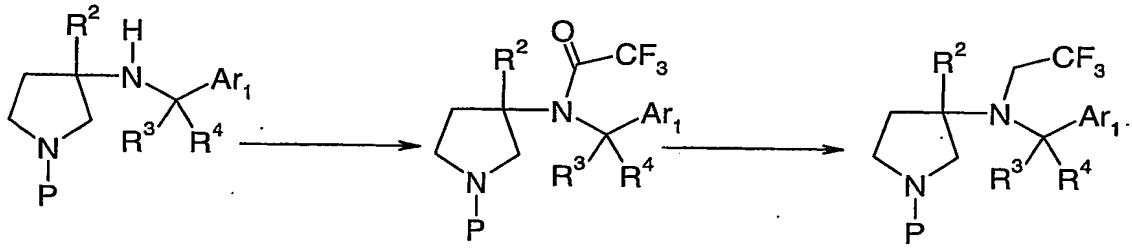
Compounds of formula (I) wherein R^1 is –CH_2-COO-(C_1-C_2 alkyl) can be prepared by reacting intermediate (V) with a compound of formula L_2-CH_2-COO-(C_1-C_2 alkyl) wherein L_2 is a suitable leaving group such as for example bromo, chloro or iodo. Said reaction can be carried out in the presence of a suitable base such as sodium hydride, in a suitable solvent such as dimethylformamide.



(V) $(VIII)_b$

Scheme 5

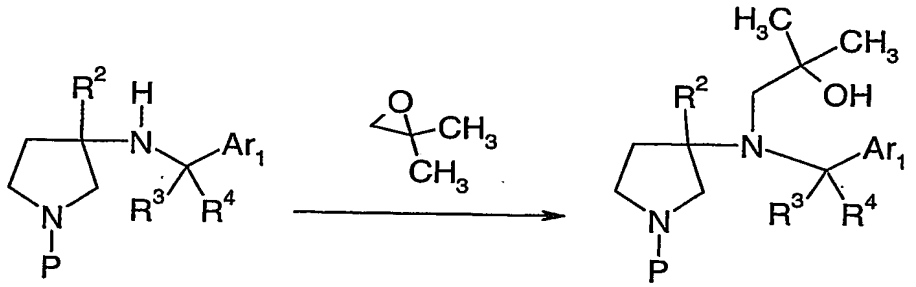
Compounds of formula (I) wherein R^1 is $-(CH_2)_m-CF_3$ can be prepared by reacting intermediate (V) with a compound of formula $HOOC-(CH_2)_{m_1}-CF_3$, wherein m_1 is 0, 1 or 2. The acid may be activated as its anhydride or acyl chloride, and is reacted in the presence of a suitable base such as triethylamine and a catalytic amount of DMAP, in a suitable solvent such as DCM. The resulting amide can be reduced to the amine of formula $(VIII)_c$ in the presence of a suitable borane. For example, for compounds wherein m is 1, the reduction can be carried out in the presence of BH_3-Me_2S borane-dimethyl sulphide complex, in a suitable solvent such as THF.



(V) $(VIII)_c$

Scheme 6

Compounds of formula (I) wherein R^1 is $-(C_1-C_6$ alkylene)-OH can be prepared by reacting intermediate (V) with an epoxide. For example for compounds wherein R^1 is $-CH_2-C(CH_3)_2-OH$, the intermediate of formula (V) is reacted with 2,2-dimethyloxirane, in a suitable solvent such as aqueous ethanol.

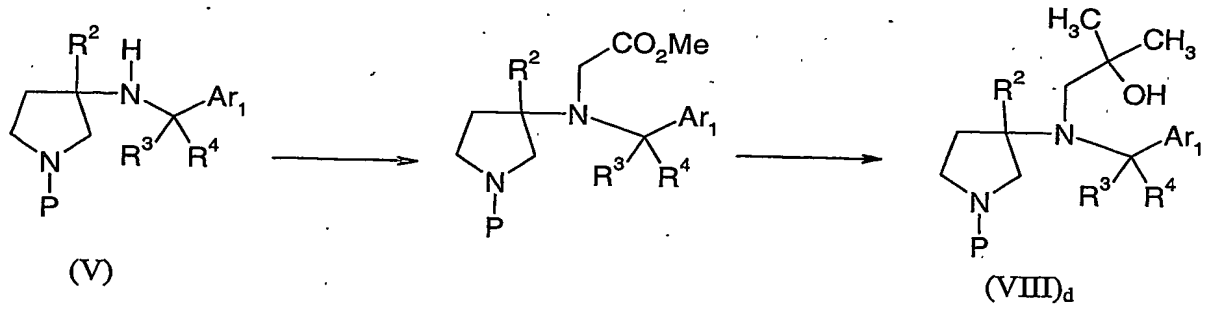


(V) $(VIII)_d$

Scheme 7

Alternatively compounds of formula (I) wehrein R^1 is $-(C_1-C_6$alkylene)-OH can be prepared by reacting intermediate (V) with an w-haloalkanoate, such as

methylbromoacetate, in the presence of a base such a sodium hydrogen carbonate in a solvent such as acetonitrile. The intermediate ester is then reacted with 2 equivalents of methyl magnesium bromide in THF to yield the tertiary alcohol(VIII)$_d$:

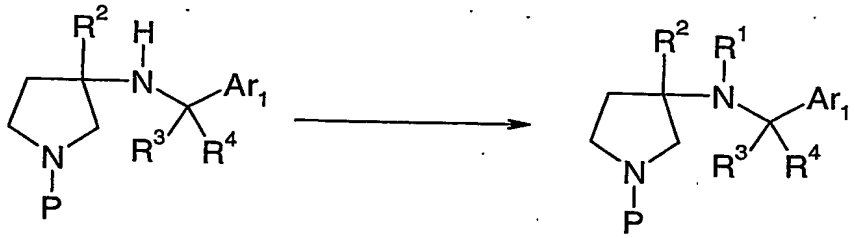


(V) (VIII)$_d$

Scheme 8

It will be appreciated that the scheme 8 above applies to alkylene chains longer than $-CH_2-$.

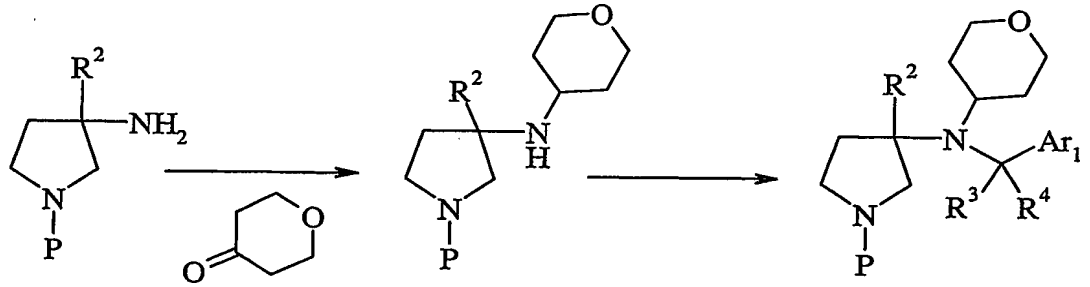
Compounds of formula (I) wherein R^1 is $-C_2-C_6$ alkenyl, $-(CH_2)_n-S-(C_1-C_3$ alkyl), $-(C_1-C_5$ alkylene)$-O-(C_1-C_3$ alkyl), $-(C_1-C_5$ alkylene)$-O-(C_3-C_6$ cycloalkyl), $-(C_1-C_5$ alkylene)$-SO_2-(C_1-C_3$ alkyl), $-(C_1-C_5$ alkylene)$-OCF_3$, or $-(C_1-C_5$ alkylene)$-CN$, can be prepared via alkylation of intermediate (V) with a compound of formula $L_2-C_2-C_6$ alkenyl, $L_2-(CH_2)_n-S-(C_1-C_3$ alkyl), $L_2-(C_1-C_5$ alkylene)$-O-(C_1-C_3$ alkyl), $L_2-(C_1-C_5$ alkylene)$-O-(C_3-C_6$ cycloalkyl), $L_2-(C_1-C_5$ alkylene)$-SO_2-(C_1-C_3$ alkyl), $L_2-(C_1-C_5$ alkylene)$-OCF_3$, or $L_2-(C_1-C_5$ alkylene)$-CN$ respectively, wherein L_2 is a suitable leaving group such as chloro, bromo, iodo or mesylate, in the presence of a suitable base such as potassium carbonate and a suitable solvent such as acetonitrile, to give the corresponding intermediate of formula (VIII)$_e$.



(V) (VIII)$_e$

Scheme 9

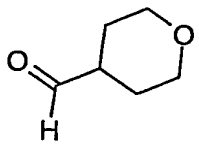
Compounds of formula (I) wherein R^1 is a group of formula (i) can be prepared using the synthesis illustrated in scheme 10 for compounds wherein R^1 is 4-tetrahydropyranyl. The compound of formula (IV) can be alkylated via reductive alkylation using standard methods, as those mentioned above with the ketone Ar_1-CO-R^3. For example compound of formula (IV) can be alkylated with 4-tetrahydropyranone in the presence of a suitable borane, such as sodium borohydride or $NaBH(OAc)_3$, optionally in the presence of an acid such as acetic acid, in the presence of a suitable solvent such as dichloroethane (DCE). Then, the secondary amine can be alkylated with a compound of formula $Ar_1CH_2L_1$ wherein L_1 is a suitable leaving group such as chloro, bromo, iodo or mesylate, in the presence of a suitable base such as potassium carbonate and a suitable solvent such as acetonitrile, to give the corresponding intermediate of formula $(VIII)_f$. It will be appreciated that as mentioned above the same reaction can be carried out using Ar_1-CR^3R^4-L_1 wherein R^3 and $R^4$are C_1-C_2 alkyl.



(IV) $(VIII)_f$

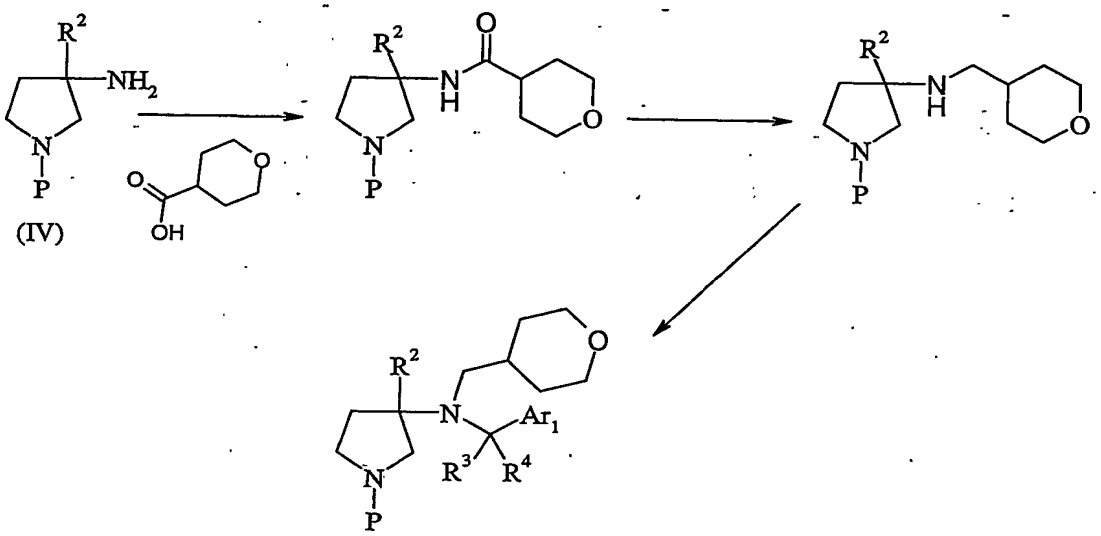
Scheme 10

It will be appreciated that for compounds of formula (I) wherein R^1 is a group of formula (i) and r is 1 then the reductive amination can be carried out using the same reaction conditions but using the corresponding homologous aldehyde of formula



instead of the corresponding 4-tetrahydropyranone. Alternatively, compounds of formula (I) wherein R^1 is a group of formula (i) and r is 1 can be prepared via formation of an

amide, followed by reduction of this amide bond to the corresponding amine as shown in scheme 11 below:

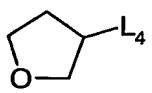


(IV) (VIII)$_g$

Scheme 11

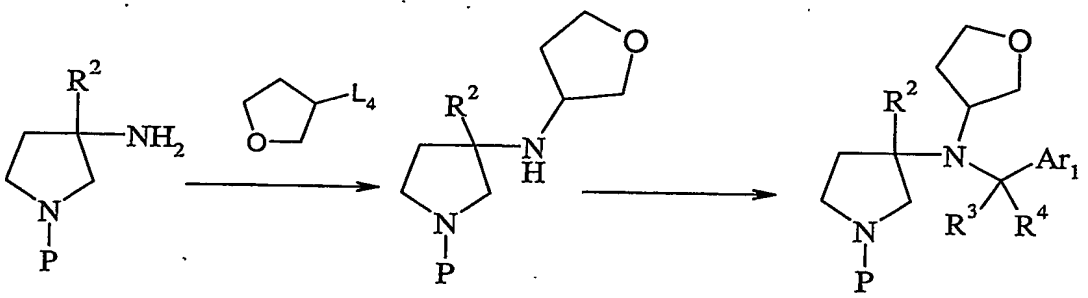
The coupling reaction can be carried out using standard methods known in the art. The reduction of the amide bond can also be carried by general methods known in the art for example using the same reduction conditions as those used in scheme 6, such as in the presence of BH_3-Me_2S (borane-dimethyl sulphide complex), in a suitable solvent such as THF.

Alternatively, compounds of formula (I) wherein R^1 is a group of formula (i) wherein r is 0 can be prepared by a process illustrated in scheme 12 for compounds wherein –Z is hydrogen, s is1, t is 2, each R^5, R^6, R^7 and R^8 are hydrogen and –X- is –O-, (i.e. R^1 is 2-tetrahydrofuranyl). The compound of formula (IV) can be alkylated with a compound of formula:



wherein L_4 is a suitable leaving group such as chloro, bromo, iodo, mesylate or tosylate, in the presence of a suitable base such as potassium carbonate and a suitable solvent such as acetonitrile, to give the corresponding secondary amine which can be subsequently alkylated with a compound of formula $Ar_1CH_2L_1$ wherein L_1 is a suitable leaving group

such as chloro, bromo, iodo or mesylate, in the presence of a suitable base such as potassium carbonate and a suitable solvent such as acetonitrile, to give the corresponding intermediate of formula $(VIII)_f$. It will be appreciated that as mentioned above the same reaction can be carried out using Ar_1-CR^3R^4-L_1 wherein R^3 and $R^4$are C_1-C_2 alkyl.

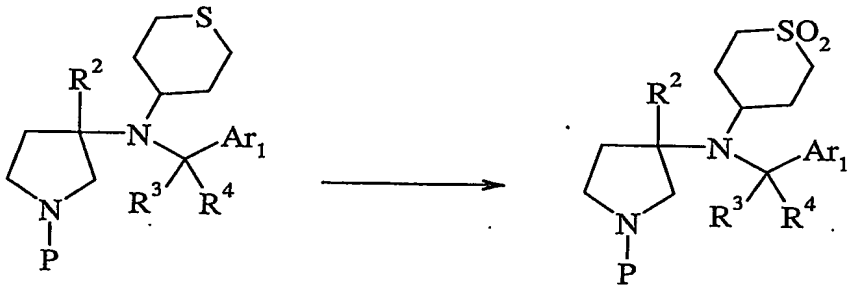


(V) $(VIII)_h$

Scheme 12

The tetrahydrofuranyl intermediates can be prepared from the corresponding 3-hydroxytetrahydrofuran, wherein the hydroxy group is converted into the leaving group using standard methods.

Compounds of formula (I) wherein R^1 is a group of formula (i) and –X- is $–SO_2-$ can be prepared from the corresponding intermediates $(VIII)_f$ wherein the thioether is oxidized to the corresponding sulphoxide as shown in scheme 13 below:

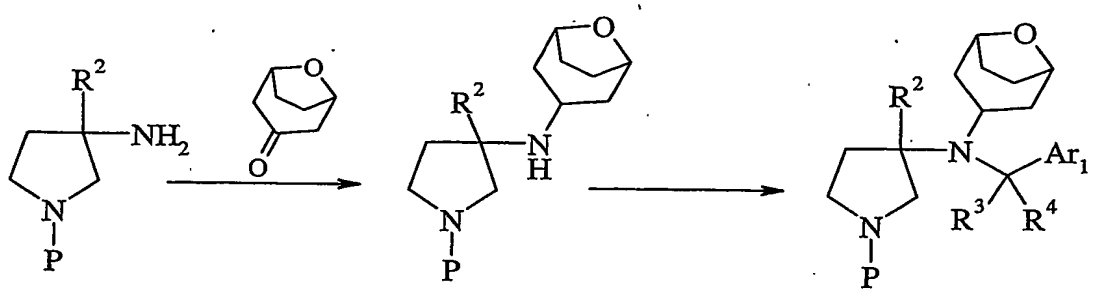


$(VIII)_f$ $(VIII)_i$

Scheme 13

Compounds of formula (I) wherein R^1 is a group of formula (ii) can be prepared using the synthesis illustrated in scheme 14 for compounds wherein R^1 is oxabicyclo[3,2,1]octan-3-yl. The compound of formula (IV) can be alkylated via reductive alkylation using

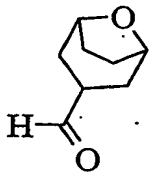
standard methods, as those mentioned above with the ketone Ar_1-CO-R^3. For example compound of formula (IV) can be alkylated with oxabicyclo[3,2,1]octan-3-one in the presence of a suitable borane, such as sodium borohydride or $NaBH(OAc)_3$, optionally in the presence of an acid such as acetic acid, in the presence of a suitable solvent such as dichloroethane (DCE). Then, the secondary amine can be alkylated with a compound of formula $Ar_1CH_2L_1$ wherein L_1 is a suitable leaving group such as chloro, bromo, iodo or mesylate, in the presence of a suitable base such as potassium carbonate and a suitable solvent such as acetonitrile, to give the corresponding intermediate of formula $(VIII)_1$. It will be appreciated that as mentioned above the same reaction can be carried out using Ar_1-CR^3R^4-L_1 wherein R^3 and R^4 are C_1-C_2 alkyl.



(IV) (VIII)$_j$

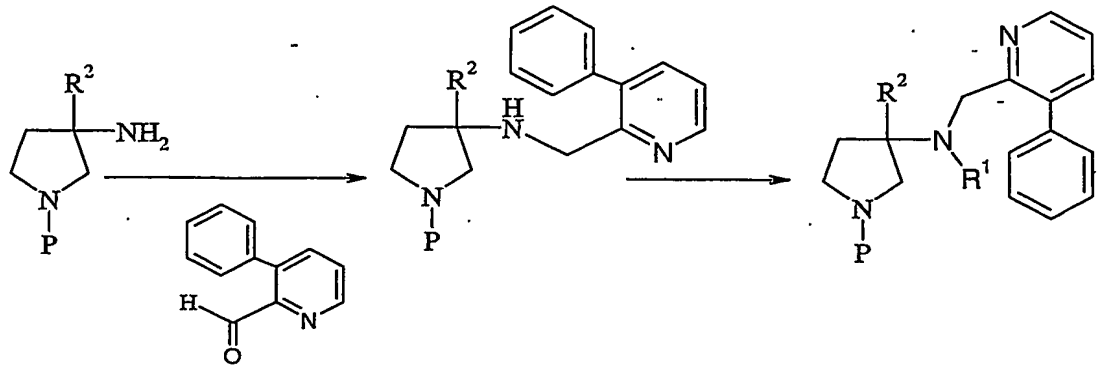
Scheme 14

The oxabicyclo[3,2,1]octan-3-one intermediate is prepared according to the method described in A E Hill, G Greenwood and H M R Hoffmann JACS 1973, 95, 1338. It will be appreciated that for compounds of formula (I) wherein R^1 is a group of formula (i) and r is 1 then the reductive amination can be carried out using the same reaction conditions but using the corresponding homologous aldehyde of formula



instead of the corresponding oxabicyclo[3,2,1]octan-3-one.

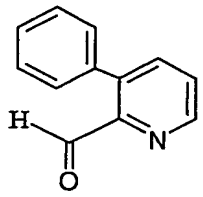
Compounds of formula (I) wherein Ar_1 is a substituted or unsubstituted pyridyl group can be prepared by a process illustrated in scheme 15 for compounds wherein R^3 and R^4 are hydrogen and Ar_1 is 3-phenylpyrid-2-yl.



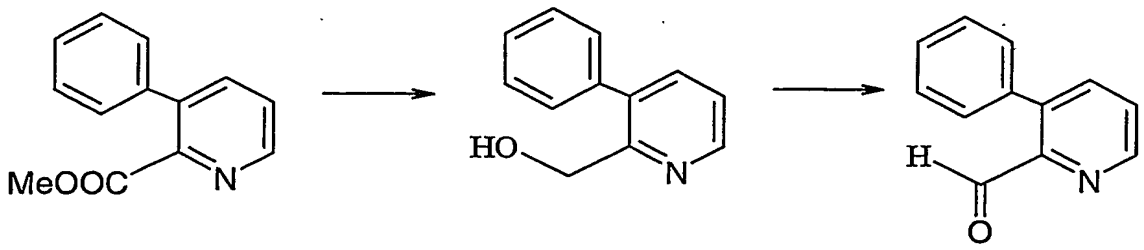
(IV) (VIII)$_k$

Scheme 15

The compound of formula (IV) can be alkylated via reductive alkylation using standard methods, as those mentioned above with the ketone Ar_1-CO-R^3. For example compound of formula (IV) can be alkylated with an aldehyde of formula:



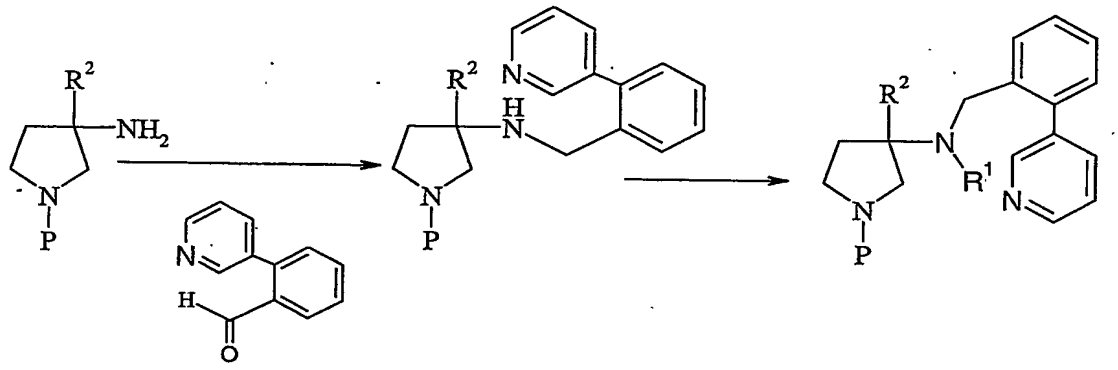
in the presence of a suitable borane, such as sodium borohydride or $NaBH(OAc)_3$, optionally in the presence of an acid such as acetic acid, in the presence of a suitable solvent such as dichloroethane (DCE). Then, the secondary amine can be alkylated using the geheral methods described above for the incorporation of R^1. The intermediate aldehyde can be prepared via reduction of readily available methyl 3-phenyl picolinate to the corresponding alcohol and subsequent oxidation to the aldehyde as shown in scheme 16 below.



scheme 16

The reduction step can be carried out in the presence of a suitable reducing agent such as lithium borohydride in a suitable solvent such as tetrahydrofuran. The oxidation to the aldehyde can be carried out under Swern conditions such as oxalyl chloride and DMSO in DCM.

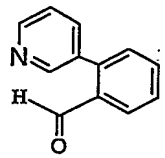
Compounds of formula (I) wherein Ar_1 is a substituted or unsubstituted phenyl group can be prepared by a process illustrated in scheme 17 for compounds wherein R^3 and R^4 are hydrogen and Ar_1 is 2-(3-pyridyl)phenyl.



(IV) (VIII)$_1$

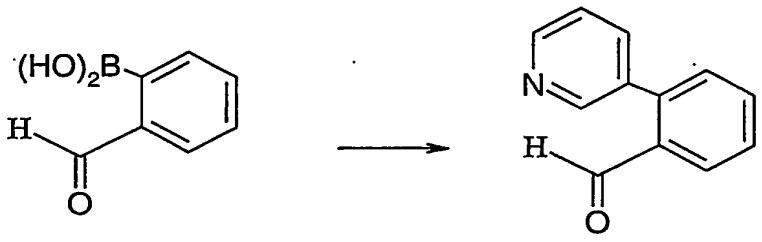
Scheme 17

The compound of formula (IV) can be alkylated via reductive alkylation using standard methods, as those mentioned above with the ketone Ar_1-CO-R^3. For example compound of formula (IV) can be alkylated with an aldehyde of formula:



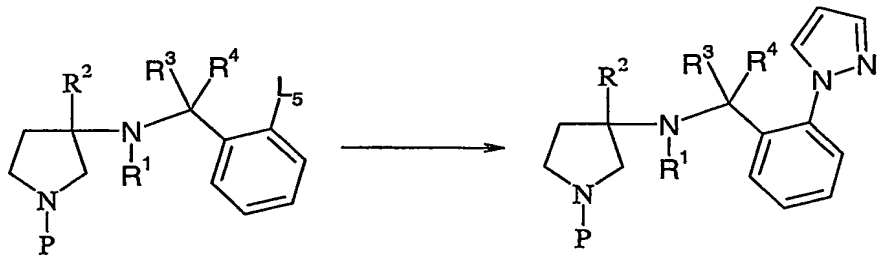
in the presence of a suitable borane, such as sodium borohydride or $NaBH(OAc)_3$, optionally in the presence of an acid such as acetic acid, in the presence of a suitable solvent such as dichloroethane (DCE). Then, the secondary amine can be alkylated using the general methods described above for the incorporation of R^1. The intermediate aldehyde can be prepared from the commercially available 2-formyl phenyl boronic acid via palladium coupling in the presence of 3-bromopyridine, a suitable palladium catalyst

such as $Pd(PPh_3)_4$ and a suitable base such as potassium carbonate in a suitable solvent such as acetonitrile, as shown in scheme 18 below.



scheme 18

Compounds of formula (I) wherein Ar_1 is a phenyl group substituted with a 1-pyrazole group can be prepared by a process illustrated in scheme 19.



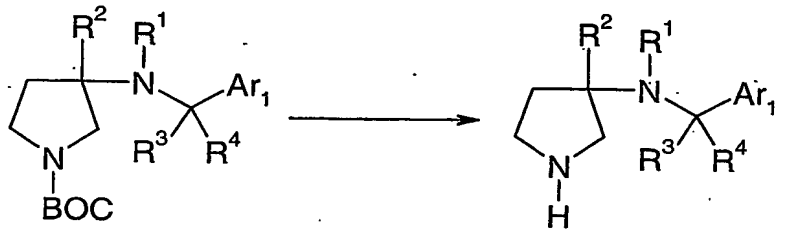
$(VIII)_{m'}$ $(VIII)_m$

Scheme 19

The pyrazole group can be incorporated by reacting a compound of formula $(VIII)_{m'}$, wherein L_5 is a suitable leaving group such as bromo, chloro or iodo, with pyrazole in the presence of a suitable base such as potassium carbonate and a catalytic amount of copper iodide in a suitable solvent such as for example DMF. The compound of formula $(VIII)_{m'}$ can be prepared by any of the methods mentioned above for compounds wherein Ar1 is a phenyl group substituted with a halogen atom such as chloro, bromo or iodo.

It will be appreciated that any of the intermediates (VIII), $(VIII)_{a-m}$ are then deprotected using suitable deprotecting conditions such as those discussed in Greene, to give the corresponding compounds of formula (I). For example if the protecting group is a boc group, the deprotection reaction can be carried out in trifluoroacetic acid in a suitable

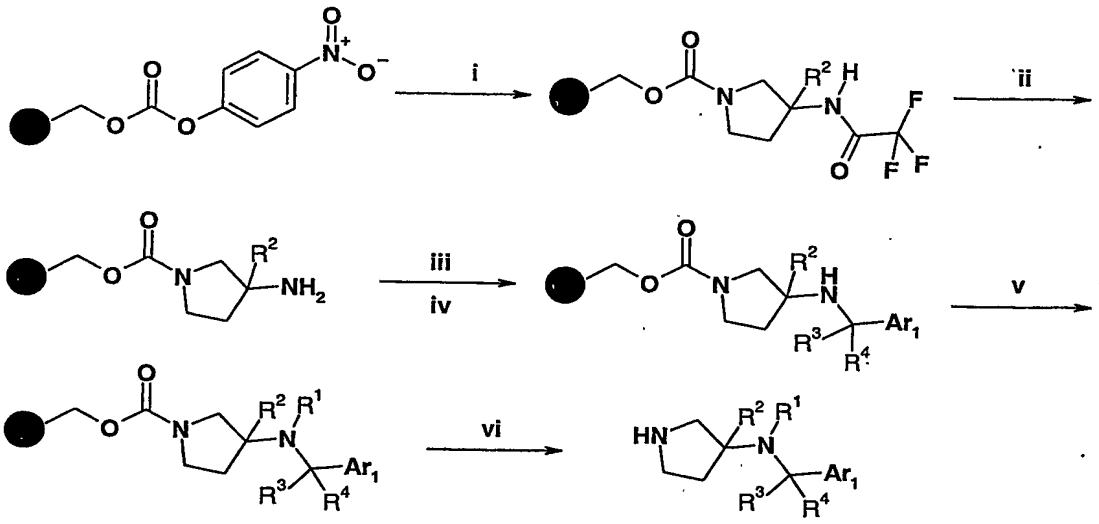
solvent such as DCM. Alternatively the reaction can be carried out in ethanolic hydrochloric acid.



(I)

Scheme 20

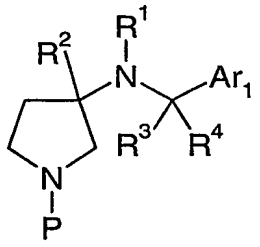
Compounds of formula (I) wherein R^3 and R^4 are both hydrogen may also be prepared by solid phase synthesis by the route shown below.



The sequence is preferably performed on a polystyrene resin. The process may be run in a combinatorial fashion such that all possible compounds from sets of precursors Ar_1CHO and R^9CHO may be prepared, wherein R^9 is chosen such that $R^9\text{-}CH_2 = R^1$, and R^1 and Ar_1 have the values defined above for formula (I). The sequence is performed without characterisation of the resin-bound intermediates. In step (i) 3-trifluoroacetamido-pyrrolidine is bound to a solid support by reaction with 4-nitrophenyl carbonate activated polystyrene resin in the presence of a base, such as N,N-diisopropylethylamine, in a solvent such as DMF. In step (ii), the trifluoroacetamido protecting group is cleaved by

hydrolysis with a base such as aqueous lithium hydroxide. In step (iii) the primary amine is then condensed with a substituted benzaldehyde in the presence of a dehydrating agent, such as trimethylorthoformate, to form the intermediate imine. In step (iv) the imine is reduced with a borane reducing agent, such as sodium cyanoborohydride, in a solvent such as DMF, containing acetic acid. In step (v) the resultant secondary amine is then reductively alkylated with an aldehyde in the presence of a reducing agent such as sodium triacetoxyborohydride in a solvent, such as DMF. In step (vi) the desired product is finally cleaved from the resin with acid, such as aqueous trifluoroacetic acid.

The present invention also provides a process for producing a compound of formula I above, which comprises deprotecting a compound of the formula (VIII) .



(VIII)

where P is an N-protecting group, optionally followed by the further step of forming a pharmaceutically salt. Suitable N-protecting groups will be known to the person skilled in the art and as described in, for example, Greene. They include, for example, boc, benzyl, benzyloxycarbonyl and acetyl.

The following Preparations and Examples illustrate routes to the synthesis of the compounds of the invention.

Preparation

1,1-Dimethylethyl (3*S*)-3-aminopyrrolidine-1-carboxylate

a) 1,1-Dimethylethyl (3*R*)-3-hydroxypyrrolidine-1-carboxylate

Solid di*tert*-butyldicarbonate (38.8g, 178mmol) was added in portions over 15 minutes to a stirred solution of (3*R*)-pyrrolidin-3-ol hydrochloride (20g, 162mmol), triethylamine (24.8mL, 178mmol) and 4-(dimethylamino)-pyridine (20mg) in dry dichloromethane (300mL). After stirring for 2 hours at room temperature, the mixture was washed with aqueous citric acid, then brine. The organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give an oil. This was purified by flash chromatography on silica, eluting with ethyl acetate/cyclohexane (20:80 to 60:40), to give the title compound as a solid.

b) 1,1-Dimethylethyl (3*R*)-3-[(methylsulfonyl)oxy]-pyrrolidine-1-carboxylate

Methanesulfonyl chloride (5.26mL, 68mmol) was added dropwise over 5 minutes to a stirred solution of 1,1-dimethylethyl (3*R*)-3-hydroxypyrrolidine-1-carboxylate (10.6g, 56.7mmol) and triethylamine (11.8mL, 85mmol) in dichloromethane (250mL) at -10°C. After stirring for 1 hour at 0°C, the reaction was quenched by addition of water. The organic phase was washed with brine, dried ($MgSO_4$), filtered and evaporated *in vacuo* to give an oil. This was purified by flash chromatography on silica, eluting with ethyl acetate/cyclohexane (25:75 to 50:50), to give the title compound as an oil.

c) 1,1-Dimethylethyl (3*S*)-3-azidopyrrolidine-1-carboxylate

Sodium azide (4.4g, 67.4mmol) was added to a solution of 1,1-dimethylethyl (3*R*)-3-[(methylsulfonyl)oxy]-pyrrolidine-1-carboxylate (14.3g, 54mmol) in dry dimethylformamide (75mL) and the resultant suspension heated at 65°C for 8 hours. After cooling to room temperature, the reaction mixture was diluted with water and extracted into diethyl ether. The organic phase was washed two further times with water, then brine. The organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give an oil. This was purified by flash chromatography on silica, eluting with diethyl ether/cyclohexane (20:80 to 40:60), to give the title compound as an oil.

d) 1,1-Dimethylethyl (3*S*)-3-aminopyrrolidine-1-carboxylate

A mixture of 1,1-dimethylethyl (3*S*)-3-azidopyrrolidine-1-carboxylate (9.0g, 2.97mmol) and 5% palladium-on-carbon (0.70g) in methanol (150mL) was hydrogenated in a Parr apparatus at 65 p.s.i. for 4 hours. The catalyst was removed by filtration through Celite and the solvent evaporated *in vacuo* to give an oil. The resultant title compound was used in subsequent reactions without further purification.

1,1-Dimethylethyl (3*R*)-3-aminopyrrolidine-1-carboxylate was similarly prepared as described above, from (3*S*)-pyrrolidin-3-ol.

Preparation

1,1-Dimethylethyl (3*S*)-3-[(1-methylethyl)amino]-pyrrolidine-1-carboxylate

A mixture of 1,1-dimethylethyl (3*S*)-3-aminopyrrolidine-1-carboxylate (3.0g) and 5% palladium-on-carbon (0.35g) in methanol (75mL) and acetone (15mL) was hydrogenated in a Parr apparatus at 65 p.s.i. for 3 hours. The catalyst was removed by filtration through Celite and the solvent evaporated *in vacuo* to give an oil. The resultant title compound was used in subsequent reactions without further purification.
^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.11-1.19 (m, 6H), 1.45 (s, 9H), 1.55-1.75 (m, 1H), 2.01-2.15 (m, 1H), 2.80-2.92 (m, 1H), 2.93-3.05 (m, 1H), 3.25-3.70 (m, 4H).

The following secondary amines were similarly prepared by reductive alkylation of 1,1-dimethylethyl (3*S*)-3-aminopyrrolidine-1-carboxylate with the appropriate aldehyde or ketone:

1,1-Dimethylethyl (3*S*)-3-(cyclopentylamino)pyrrolidine-1-carboxylate
1,1-Dimethylethyl (3*S*)-3-[(cyclohexylmethyl)amino]-pyrrolidine-1-carboxylate

Preparation

1,1-Dimethylethyl (3S)-3-({[2-(trifluoromethyl)phenyl]-methyl}amino)pyrrolidine-1-carboxylate

Method A

a)(3*S*)-*N*-{(*E*)-[2-(Trifluoromethyl)phenyl]methylidene}-pyrrolidin-3-amine

3(*S*)-Pyrrolidin-3-amine (0.45g, 5.2mmol) and trifluoromethylbenzaldehyde (0.87g, 5.0mmol), a crystal of 4-toluenesulphonic acid and toluene were refluxed with stirring for one day, using a Dean and Stark apparatus. The solution was evaporated *in vacuo* to give the title compound as a brown oil (M+H = 243).

b) 1,1-Dimethylethyl (3S)-3-({(E)-[2-(trifluoromethyl)-phenyl]methylidene}amino)pyrrolidine-1-carboxylate

(3*S*)-*N*-{(*E*)-[2-(Trifluoromethyl)phenyl]methylidene}-pyrrolidin-3-amine (1.21g, 5mmol) was dissolved in dichloromethane (50 mL), and di-*tert*-butyl dicarbonate (1.1g, 5.05mmol) followed by DMAP (60mg; 0.5mmol) was added. After stirring under nitrogen for 4 hours, the solution was evaporated *in vacuo* to give the title compound as a brown oil (M + H = 343).

c) 1,1-Dimethylethyl (3*S*)-3-({[2-(trifluoromethyl)-phenyl]methyl}amino)pyrrolidine-1-carboxylate

1,1-Dimethylethyl (3*S*)-3-({(*E*)-[2-(trifluoromethyl)-phenyl]methylidene}amino)pyrrolidine-1-carboxylate (1.71g, 5mmol) was hydrogenated in the presence of 5% palladium on carbon (250mg) at 65psi in ethanol (60mL). After 3.5

hours, the catalyst was filtered off and the filtrate evaporated *in vacuo* to give an oil. The oil was purified by automated flash chromatography over silica, eluting with 10% ethyl acetate in cyclohexane (10:90 to 50:50), to give the title compound as a colourless oil (1.0g, 58%; M + H = 345).

Method B

a) (3*S*)-*N*-{[2-(Trifluoromethyl)phenyl]methyl}pyrrolidin-3-amine

A mixture of 3(*S*)-pyrrolidin-3-amine (4g, 46.5mmol), 2-trifluoromethylbenzaldehyde (9.1g, 46.5mmol), 5% palladium on carbon (0.4g) and ethanol (150mL) was hydrogenated at 60psi for 3 hours using a Parr hydrogenator. The catalyst was filtered off and the filtrate evaporated *in vacuo* to give the title compound as an oil. MS: [M+H] = 245.

b) 1,1-Dimethylethyl (3*S*)-3-({[2-(trifluoromethyl)-phenyl]methyl}amino)pyrrolidine-1-carboxylate

(3*S*)-*N*-{[2-(Trifluoromethyl)phenyl]methyl}pyrrolidin-3-amine (12g, 49.2mmol) was dissolved in dichloromethane (120 mL), then di-*tert*-butyl dicarbonate (10.7g, 49.2mmol) and DMAP (40mg, 0.33mmol) were added. After stirring under nitrogen for 1 day, the solution was evaporated *in vacuo* to give an oil. The oil was purified by automated flash chromatography over silica, eluting with ethyl acetate in cyclohexane (0:100 to 40:60), to give the title compound as a colourless oil.

MS: [M+H] = 345.

Preparation

1,1-Dimethylethyl (3*S*)-3-({[4-fluoro-2-(trifluoromethyl)-phenyl]methyl}amino)pyrrolidine-1-carboxylate

1,1-Dimethylethyl (3*S*)-3-aminopiperidine-1-carboxylate (5g) and 4-fluoro-2-(trifluoromethyl)benzaldehyde (5.15g, 26.8mmol)were allowed to stir in methanol for 16h at room temperature. Sodium borohydride (1.62g, 26.8mmol) was then added portionwise. The resulting solution was further stirred for 2 h at room temperature. The solvent was evaporated *in vacuo,* water was added, and the solution extracted with dichloromethane. The organic extracts were absorbed onto a methanol washed cationic ion exchange resin (Isolute ™ SCX-2). The basic components were recovered from the column by elution with 7N ammonia in methanol. The resultant solution was concentrated *in vacuo* to yield the desired compound as an oil. This was further purified by column chromatography on silica gel, eluting with ethyl acetate/iso-hexane (0:100 to 40:60). The title compound was used in subsequent reactions without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.37-7.28 (m, 2H), 7.24-7.20 (m, 1H), 3.80 (s, 2H), 3.52-3.48 (m, 2H), 3.32 (m, 3H), 3.12 (m, 1H), 2.08-2.0 (m, 1H), 1.75 (m, 1H), 1.45 (s, 9H).

The following secondary amines were similarly prepared by reductive alkylation of 1,1-dimethylethyl (3*S*)-3-aminopiperidine-1-carboxylate with the appropriate benzaldehyde:

1,1-Dimethylethyl (3*S*)-3-{[(3,5-dichloro-phenyl)methyl]-amino}pyrrolidine-1-carboxylate.

1,1-Dimethylethyl (3*S*)-3-{[(5-fluoro-2-(trifluoromethyl)-phenyl)methyl]amino}pyrrolidine-1-carboxylate.

1,1-Dimethylethyl (3*S*)-3-{[(2-chloro-4-fluoro-phenyl)-methyl]amino}pyrrolidine-1-carboxylate.

Example 1

(3*S*)-*N*-(1-Methylethyl)-*N*-{[3,5-dichlorophenyl]-methyl}pyrrolidin-3-amine *D*-tartrate

a) 1,1-Dimethylethyl (3*S*)-3-((1-methylethyl)-{[3,5-dichlorophenyl]methyl}amino)-pyrrolidine-1-carboxylate

To a solution of 1,1-dimethylethyl (3*S*)-3-[(1-methylethyl)amino]-pyrrolidine-1-carboxylate (1g, 4.4 mmol) and 3,5-dichlorobenzaldehyde (1.53g, 8.77 mmol) in trimethylorthoformate (10 mL) at room temperature under a nitrogen atmosphere was added portionwise sodium triacetoxyborohydride (1.3g, 6.1 mmol). The reaction was stirred at room temperature for 72 hours, then evaporated to dryness *in vacuo*. The residue was taken up in aqueous saturated sodium hydrogen carbonate/dichloromethane mixture. The aqueous layer was further extracted with dichloromethane (3X), and the combined organic layers dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The resulting residue was dissolved in methanol and filtered through a cationic ion exchange resin (Isolute ™ SCX-2). The basic components were recovered from the column by elution with 2N ammonia in methanol. This solution was concentrated *in vacuo* to yield the desired compound as a yellow oil that was used in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.95-1.04 (m, 6H), 1.45 (s, 9H), 1.56-1.77 (m, 1H), 1.8-1.94 (m, 1H), 2.9-3.09 (m, 2H), 3.11-3.25 (m, 1H), 3.32-3.56 (m, 3H), 3.59 (s, 2H), 7.15-7.27 (m, 3H). MS: [M+H] = 387/389/391.

b)(3*S*)-*N*-(1-Methylethyl)-*N*-{[3,5-dichlorophenyl]methyl}-pyrrolidin-3-amine *D*-tartrate

1,1-Dimethylethyl (3*S*)-3-((1-methylethyl)-{[3,5-dichlorophenyl]methyl}amino)pyrrolidine-1-carboxylate (1.36g, 3.51 mmol) was dissolved in a mixture of dichloromethane and trifluoroacetic acid (10 mL, 2:1) and stirred at room temperature for 30 minutes. The reaction solution was concentrated *in vacuo* and redissolved in MeOH. This solution was filtered through a cationic ion exchange resin (Isolute ™ SCX-2). The basic components were isolated by elution with 2N ammonia in methanol and further purified by UV guided prep-LC. The desired compound was isolated from the acidic prep-LC mobile phase *via* a cationic ion exchange resin as described above. After evaporation *in vacuo* the residue was dissolved in hot

cyclohexane (5 mL) and to this was added an equimolar amount of D-tartaric acid (450 mg), dissolved in a minimal amount of hot isopropanol. The solution was evaporated *in vacuo* to yield the title compound as a solid.

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 0.95-0.99 (m, 6H), 1.58-1.71 (m, 1H), 1.91-2.00 (m, 1H), 2.76-2.91 (m, 2H), 2.97-3.07 (m, 1H), 3.18-3.25 (m, 2H), 3.55-3.67 (m, 4H), 3.95 (s, 2H), 7.37-7.38 (m, 2H), 7.43-7.45 (m, 1H). MS: [M+H] = 287/289/291.

The following Examples were similarly prepared as described above for Example 1, by reductive alkylation of 1,1-dimethylethyl (3*S*)-3-[(1-methylethyl)amino]-pyrrolidine-1-carboxylate with the appropriate substituted benzaldehyde:

Example 2

(3*S*)-*N*-(1-Methylethyl)-*N*-{[2-(methylthio)phenyl]methyl}-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 0.99 (s, 6H), 2.06 (m, 1H), 2.37 (s, 3H), 3.01-2.85 (m, 1H), 3.18-3.06 (m, 1H), 3.46-3.19 (m, 4H), 3.67 (dd, 2H), 6.60 (s, 2H), 7.10-7.02 (m, 1H), 7.20-7.11 (m, 2H), 7.40 (dd, 1H); MS: [M+H] = 265.

Example 3

(3*S*)-*N*-(1-Methylethyl)-*N*-{[2-trifluoromethyl)oxy]-phenyl}methyl)pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 1.10 (s, 6H), 1.99-1.82 (m, 1H), 2.30-2.05 (m, 1H), 3.10-2.93 (m, 1H), 3.29-3.16 (m, 1H), 3.39-3.32 (m, 4H), 3.73 (s, 2H), 6.69 (s, 2H), 7.13 (d, 1H), 7.44-7.34 (m, 3H); MS: [M+H] = 303.

Example 4

(3*S*)-*N*-[(3,5-Dimethylphenyl)methyl]-*N*-(1-methylethyl)-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 1.14 (d, 6H), 2.05-1.92 (m, 1H), 2.22-2.11 (m, 1H), 2.34 (s, 6H), 3.16-2.99 (m, 1H), 3.55-3.20 (m, 1H), 3.42-3.32 (m, 4H), 3.94-3.63 (m, 2H), 6.75 (s, 2H), 6.92 (s, 1H), 7.03 (s, 2H); MS: [M+H] = 247.

Example 5

(3*S*)-*N*-[(3-Chlorophenyl)methyl]-*N*-(1-methylethyl)-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 0.87 (dd, 6H), 1.86-1.69 (m, 1H), 2.04-1.94 (m, 1H), 2.96-2.80 (m, 1H), 3.14-3.04 (m, 1H), 3.20-3.17 (m, 4H), 3.59 (s, 2H), 6.56 (s, 2H), 7.11-7.08 (m, 1H), 7.18-7.14 (m, 2H), 7.29 (s, 1H); MS: [M+H] = 253/255.

Example 6

(3*S*)-*N*-[(2,3-Dichlorophenyl)methyl]-*N*-(1-methylethyl)-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 1.12 (dd, 6H), 1.96-1.82 (m, 1H), 2.18-2.05 (m, 1H), 3.11-2.98 (m, 1H), 3.27-3.17 (m, 1H), 3.41-3.31 (m, 4H), 3.92 (m, 2H), 6.70 (s, 2H), 7.33 (t, 1H), 7.45 (d, 1H), 7.67 (d, 1H); MS: [M+H] = 288.

Example 7

(3*S*)-*N*-[(2,3-Dimethylphenyl)methyl]-*N*-(1-methylethyl)-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 1.09 (d, 6H), 2.15-1.92 (m, 2H), 2.29 (s, 3H), 3.08-2.96 (m, 1H), 3.26-3.15 (m, 1H), 3.40-3.31 (m, 4H), 3.38-3.67 (m, 2H), 6.70 (s, 2H), 7.03 (dd, 1H), 7.35-7.31 (m, 1H), 7.37-7.32 (m, 1H); MS: [M+H] = 247.

Example 8

(3*S*)-*N*-[(2,4-Dichlorophenyl)methyl]-*N*-(1-methylethyl)-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 0.92-1.06 (m, 6H), 1.59-1.76 (m, 1H), 1.89-2.02 (m, 1H), 2.78-2.92 (m, 2H), 2.98-3.07 (m,1H), 3.15-3.28 (m, 2H), 3.60-3.74 (m, 3H), 3.94 (s, 2H), 7.42 (dd, 1H), 7.56 (d, 1H), 7.62 (d, 1H); MS: [M+H] = 287/289/291.

The following Examples were similarly prepared as described above for Example 1, by reductive alkylation of 1,1-dimethylethyl (3*S*)-3-[(cyclohexylmethyl)amino]-pyrrolidine-1-carboxylate with the appropriate substituted benzaldehyde:

Example 9

(3*S*)-*N*-(Cyclohexylmethyl)-*N*-[(2-methylphenyl)methyl]-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 1.20-0.73 (m, 5H), 1.42-1.34 (m, 1H), 1.88-1.66 (m, 5H), 2.04-1.94 (m, 2H), 2.18-2.08 (m, 2H), 2.33 (d, 2H), 2.48(s, 3H), 3.24-3.13 (m, 1H), 3.44-3.33 (m, 4H), 3.81-3.48 (m, 2H), 6.70 (s, 2H), 7.15 (t, 1H), 7.43 (d, 1H), 7.46 (m, 2H); MS: [M+H] = 287.

Example 10

(3*S*)-*N*-(Cyclohexylmethyl)-*N*-{[2-(methylthio)phenyl]-methyl}pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 0.86-0.69 (s, 3H), 1.22-1.12 (m, 3H), 1.41-1.29 (m, 1H), 1.84-1.67 (m, 5H), 2.16-1.95 (m, 2H), 2.34 (d, 2H), 2.38 (s, 3H), 3.23-3.05 (m, 1H), 3.44-3.28 (m, 4H), 3.78-3.55 (m, 2H), 6.70 (s, 2H), 7.16 (s, 2H), 7.35-7.32 (m, 1H); MS: [M+H] = 319.

Example 11

(3*S*)-*N*-(Cyclohexylmethyl)-*N*-[(2-fluorophenyl)methyl]-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 0.83-0.75 (s, 6H), 1.24-1.17 (m, 3H), 1.48-1.42 (m, 1H), 1.85-1.68 (m, 5H), 2.03-1.92 (m, 1H), 2.17-2.10 (m, 1H), 2.35 (d, 2H), 3.25-3.05 (m, 1H), 3.44-3.32 (m, 4H), 3.81-3.62 (m, 2H), 6.71 (s, 2H), 7.20-7.05 (m, 2H), 7.33-7.27 (m, 1H), 7.47-7.42 (m, 1H); MS: [M+H] = 291.

Example 12

(3*S*)-*N*-(Cyclohexylmethyl)-*N*-(naphthalene-1-ylmethyl)-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 1.20-0.76 (m, 5H), 1.42-1.35 (m, 1H), 1.87-1.65 (m, 5H), 2.17-1.99 (m, 2H), 2.44-2.40 (d, 2H), 3.44-3.07 (m, 4H), 3.68-3.60 (m, 1H), 4.24 (q, 2H), 6.70 (s, 2H), 7.59-7.42 (m, 4H), 7.90-7.81 (m, 2H), 8.29-8.26 (m, 1H); MS: [M+H] = 323.

Example 13

(3*S*)-*N*-[(2-Chlorophenyl)methyl]-*N*-(cyclohexylmethyl)-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 0.89-0.77 (m, 2H), 1.24-1.13 (m, 3H), 1.36 (d, 6H) , 1.49-1.42 (m, 1H), 1.83-1.68 (m, 5H), 2.15-1.93 (m, 2H), 2.35 (d, 2H), 3.20-3.06 (m, 1H), 3.33-3.23 (m, 4H), 3.75-3.42 (m, 2H), 4.69-4.61 (m, 1H), 6.70 (s, 2H), 6.98-6.88 (m, 2H), 7.35 (d, 1H), 7.50-7.19 (m, 1H); MS: [M+H] = 307.

Example 14

(3*S*)-*N*-(Cyclohexylmethyl)-*N*-({2-[1-(methylethyl)oxy]-phenyl}methyl)pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 0.89-0.77 (m, 2H), 1.24-1.13 (m, 3H), 1.36-1.34 (dd, 6H), 1.49-1.42 (m, 1H), 1.83-1.68 (m, 5H), 1.93 (m, 2H, m), 2.35 (d, 2H), 3.20-3.06

3.20-3.06 (m, 1H), 3.33-3.23 (m, 4H), 3.75-3.42 (m, 2H), 4.69-4.61 (m, 1H), 6.70 (s, 2H), 6.98-6.88 (m, 2H), 7.35 (d, 1H), 7.50-7.19 (m, 1H); MS: [M+H] = 331.

The following Examples were similarly prepared as described above for Example 1, by reductive alkylation of 1,1-dimethylethyl (3*S*)-3-(cyclopentylamino)pyrrolidine-1-carboxylate with the appropriate substituted benzaldehyde:

Example 15

(3*S*)-*N*-Cyclopentyl-*N*-[(2,4-dichlorophenyl)methyl]-pyrrolidin-3-amine di-D-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.19-1.35 (m, 2H), 1.36-1.75 (m, 7H), 1.93-2.06 (m, 1H), 2.81-2.88 (m, 1H), 2.98-3.08 (m, 1H), 3.10-3.31 (m, 3H), 3.62-3.73 (m, 3H), 4.15 (s, 4H), 7.42 (dd, 1H), 7.55 (d, 1H), 7.62 (d, 1H); MS: [M+H] = 313/315/317.

Example 16

(3*S*)-*N*-Cyclopentyl-*N*-{[2-(trifluoromethyl)phenyl]methyl}-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.20-1.73 (m, 9H), 1.95-2.02 (m, 1H), 2.79-2.86 (m, 1H), 2.96-3.05 (m, 1H), 3.14-3.27 (m, 3H), 3.62-3.73 (m, 1H), 3.81 (s, 2H), 6.46 (s, 2H), 7.39-7.44 (m, 1H), 7.63-7.68 (m, 2H), 7.90-7.92 (m, 1H). MS: [M+H] = 313.

Example 17

(3*S*)-*N*-Cyclopentyl-*N*-[(3-chlorophenyl)methyl]-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.25-1.70 (m, 9H), 1.90-2.00 (m, 1H), 2.73-2.89 (m, 1H), 2.94-3.04 (m, 1H), 3.11-3.23 (m, 3H), 3.56-3.73 (m, 3H), 6.47 (s, 2H), 7.24-7.36 (m, 4H). MS: [M+H] = 279/281.

Example 18

(3*S*)-*N*-Cyclopentyl-*N*-[(2-chlorophenyl)methyl]-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.20-1.75 (m, 9H), 1.93-2.03 (m, 1H), 2.81-2.87 (m, 1H), 2.96-3.06 (m, 1H), 3.14-3.27 (m, 3H), 3.63-3.73 (m, 3H), 6.48 (s, 2H), 7.20-7.26 (m, 1H), 7.30-7.39 (m, 2H), 7.60-7.63 (m, 1H). MS: [M+H] = 279/281.

Example 19

(3*S*)-*N*-Cyclopentyl-*N*-{[4-(trifluoromethyl)phenyl]methyl}-pyrrolidin-3-amine acetate

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.25-1.82 (m, 9H), 1.90-2.02 (m, 4H), 2.79-2.86 (m, 1H), 2.95-3.04 (m, 1H), 3.14-3.26 (m, 3H), 3.58-3.69 (m, 1H), 3.73 (s, 2H), 7.44 (d, 2H), 7.53 (d, 2H). MS: [M+H] = 313.

Example 20

(3*S*)-*N*-Cyclopentyl-*N*-{[2-(methylthio)phenyl]methyl}-pyrrolidin-3-amine

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.33-2.02 (m, 10H), 2.45 (s, 3H), 2.81-2.88 (m, 1H), 2.98-3.08 (m, 1H), 3.13-3.30 (m, 3H), 3.58-3.71 (m, 3H), 7.09-7.23 (m, 3H), 7.54-7.57 (m, 1H). MS: [M+H] = 291.

Example 21

(3*S*)-*N*-Cyclopentyl-*N*-{[3-(trifluoromethyl)phenyl]methyl}-pyrrolidin-3-amine acetate

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.28-1.85 (m, 9H), 1.91 (s, 3H), 1.94-2.05 (m, 1H), 2.83-2.89 (m, 1H), 2.98-3.08 (m, 1H), 3.61-3.79 (m, 1H), 3.74 (s, 2H), 7.34-7.59 (m, 4H). MS: [M+H] = 313.

Example 22

(3*S*)-*N*-Cyclopentyl-*N*-{[5-fluoro-2-(trifluoromethyl)-phenyl]methyl}-pyrrolidin-3-amine

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.18-1.91 (m, 10H), 1.97-2.04 (m, 1H), 2.83-2.90 (m, 1H), 3.04-3.32 (m, 4H), 3.62-3.73 (m, 1H), 3.81 (s, 1H), 6.93-6.99 (m, 1H), 7.55-7.66 (m, 2H). MS: [M+H] = 331.

Example 23

(3*S*)-*N*-Cyclopentyl-*N*-{[2-(difluoromethoxy)phenyl]methyl}-pyrrolidin-3-amine acetate

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.35-2.03 (m, 13H), 2.80-2.87 (m, 1H), 2.98-3.07 (m, 1H), 3.16-3.27 (m, 3H), 3.59-3.72 (m, 3H), 6.54 (t, 1H), 7.03-7.05 (m, 1H), 7.15-7.24 (m, 2H), 7.58-7.61 (m, 1H). MS: [M+H] = 311.

Example 24

(3*S*)-*N*-Cyclopentyl-*N*-{[5-fluoro-2-(trifluoromethyl)-phenyl]methyl}-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.20-1.78 (m, 9H), 1.91-1.96 (m, 1H), 2.78-2.92 (m, 1H), 2.96-3.08 (m, 1H), 3.14-3.35 (m, 3H), 3.65-3.78 (m, 1H), 3.82 (s, 2H), 6.42 (s, 2H), 7.20-7.32 (m, 1H), 7.60-7.81 (m, 2H); MS: [M+H] = 331.

Example 25

(3*S*)-*N*-Cyclopentyl-*N*-[(2,4-dimethylphenyl)methyl]-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.20-1.78 (m, 9H), 1.91-1.96 (m, 1H), 2.22 (s, 6H), 2.80-2.87 (m, 1H), 2.96-3.05 (m, 1H), 3.14-3.24 (m, 3H), 3.50-3.68 (m, 3H), 3.86 (s, 2H), 6.91-6.96 (m, 2H), 7.30-7.33 (m, 1H). MS: [M+H]= 273.

Example 26

(3*S*)-*N*-Cyclopentyl-*N*-[(3,5-dimethylphenyl)methyl]-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.20-1.76 (m, 9H), 1.85-2.02 (m, 1H), 2.23 (s, 6H), 2.77-2.84 (m, 1H), 2.93-3.03 (m, 1H), 3.13-3.19 (m, 3H), 3.50-3.62 (m, 3H), 6.43-6.45 (m, 2H), 6.81 (bs, 1H), 6.91 (bs, 2H). MS: [M+H] = 273.

Example 27

(3*S*)-*N*-Cyclopentyl-*N*-[(2,5-dimethylphenyl)methyl]-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.20-1.78 (m, 9H), 1.85-1.96 (m, 1H), 2.20 (s, 3H), 2.24 (s, 3H), 2.81-2.87 (m, 1H), 2.93-3.02 (m, 1H), 3.13-3.23 (m, 3H), 3.51-3.70 (m, 3H), 6.42-6.44 (m, 2H), 6.88 (d, 1H), 6.97 (d, 1H), 7.26 (s, 1H); MS: [M+H] = 273.

Example 28

(3*S*)-*N*-Cyclopentyl-*N*-[(2,4-difluorophenyl)methyl]-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.20-1.78 (m, 9H), 1.85-1.96 (m, 1H), 2.20 (s, 3H), 2.24 (s, 3H), 2.81-2.87 (m, 1H), 2.93-3.02 (m, 1H), 3.13-3.23 (m, 3H), 3.51-3.70 (m, 3H), 6.42-6.44 (m, 2H), 6.88 (d, 1H), 6.97 (d, 1H), 7.26 (s, 1H). MS: [M+H] = 273.

Example 29

(3*S*)-*N*-Cyclopentyl-*N*-{[5-fluoro-3-(trifluoromethyl)-phenyl]methyl}-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.20-1.69 (m, 9H), 1.92-2.01 (m, 1H), 2.78-2.85 (m, 1H), 2.93-3.03 (m, 1H), 3.13-3.25 (m, 3H), 3.58-3.69 (m, 1H), 3.80 (s, 2H), 6.42-6.44 (m, 2H), 7.47-7.53 (m, 3H). MS: [M+H] = 331.

Example 30

(3*S*)-*N*-Cyclopentyl-*N*-[(3-methylphenyl)methyl]-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.20-1.76 (m, 9H), 1.90-1.96 (m, 1H), 2.28 (s, 3H), 2.77-2.84 (m, 1H), 2.93-3.03 (m, 1H), 3.15-3.41 (m, 3H), 3.55-3.67 (m, 3H), 6.42-6.44 (m, 2H), 6.98-7.01 (m, 1H), 7.10-7.20 (m, 3H). MS: [M+H] = 259.

Example 31

(3*S*)-*N*-Cyclopentyl-*N*-[(2,3-dimethylphenyl)methyl]-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.33-1.75 (m, 9H), 1.90-1.94 (m, 1H), 2.15 (s, 3H), 2.23 (s, 3H), 2.80-2.87 (m, 1H), 2.96-3.05 (m, 1H), 3.15-3.24 (m, 3H), 3.62-3.67 (m, 3H), 3.84 (s, 2H), 6.98-7.06 (m, 2H), 7.31-7.33 (m, 1H). MS: [M+H]= 273.

Example 32

(3*S*)-*N*-Cyclopentyl-*N*-[(2,3-dichlorophenyl)methyl]-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.20-1.75 (m, 9H), 1.90-2.05 (m, 1H), 2.79-2.86 (m, 1H), 2.97-3.06 (m, 1H), 3.15-3.28 (m, 3H), 3.64-3.76 (m, 3H), 3.84 (s, 2H), 7.34-7.39 (m, 1H), 7.50-7.53 (m, 1H), 7.60-7.62 (m, 1H). MS: [M+H] = 313/315/317.

Example 33

(3*S*)-*N*-Cyclopentyl-*N*-[(2-chloro-6-fluorophenyl)methyl]-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.39-1.70 (m, 8H), 1.91-1.96 (m, 2H), 3.01-3.19 (m, 4H), 3.24-3.32 (m, 1H), 3.56-3.67 (m, 1H), 3.78 (s, 2H), 3.87 (s, 2H), 7.17-7.24 (m, 1H), 7.30-7.41 (m, 2H). MS: [M+H]= 297/299.

Example 34

(3*S*)-*N*-Cyclopentyl-*N*-[(3,5-difluorophenyl)methyl]-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.30-1.69 (m, 9H), 1.95-2.00 (m, 1H), 2.78-2.85 (m, 1H), 2.96-3.06 (m, 1H), 3.11-3.27 (m, 3H), 3.56-3.70 (m, 3H), 3.87 (s, 2H), 7.01-7.05 (m, 3H). MS: [M+H]= 281.

Example 35

(3*S*)-*N*-Cyclopentyl-*N*-[(3,5-dichlorophenyl)methyl]-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.15-1.74 (m, 9H), 1.90-2.02 (m, 1H), 2.77-2.84 (m, 1H), 2.97-3.06 (m, 1H), 3.11-3.27 (m, 3H), 3.55-3.69 (m, 3H), 3.89 (s, 2H), 7.36 (d, 2H), 7.43 (d, 1H). MS: [M+H] = 313/315.

Example 36

(3*S*)-*N*-Cyclopentyl-*N*-{[2-chloro-3-(trifluoromethyl)-phenyl]methyl}-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.20-1.72 (m, 9H), 1.96-2.04 (m, 1H), 2.82-2.89 (m, 1H), 2.98-3.07 (m, 1H), 3.16-3.31 (m, 3H), 3.69-3.75 (m, 1H), 3.83 (s, 2H), 3.93 (s, 2H), 7.53-7.58 (m, 1H), 7.72-7.75 (m, 1H), 7.94-7.97 (m, 1H). MS: [M+H] = 347/349.

The following Examples were similarly prepared as described above for Example 1, by reductive alkylation of 1,1-dimethylethyl (3*S*)-3-(propylamino)pyrrolidine-1-carboxylate with the appropriate substituted benzaldehyde:

Example 37

(3*S*)-*N*-[2-Chlorophenyl)methyl]-*N*-propylpyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 0.75 (t, 3H), 1.32-1.45 (m, 2H), 1.82-1.95 (m, 1H), 2.01-2.12 (m, 1H), 2.42-2.47 (m, 2H), 3.00-3.34 (m, 4H), 3.55 (quintet, 1H), 3.71 (q, 2H), 6.58 (s, 2H), 7.11-7.28 (m, 3H), 7.47 (d,d, 1H); MS: [M+H] = 253/255.

Example 38

(3*S*)-*N*-Propyl-*N*-{2-(trifluoromethyl)phenyl]methyl}- pyrrolidin-3-amine, *D*-tartrate

^{1}H NMR: see Example 199 for data of L-tartrate; MS: [M+H] = 287.

Example 39

(3*S*)-*N*-{5-Fluoro-2-(trifluoromethyl)phenyl]methyl}-*N*-propylpyrrolidin-3-amine, *D*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 0.91 (t, 3H), 1.45-1.58 (m, 2H), 1.90-2.03 (m, 1H), 2.13-2.23 (m, 1H), 2.57-2.62 (m, 2H), 3.10-3.17 (m, 1H), 3.22-3.30 (m, 1H), 3.40-3.48 (m, 2H), 3.68 (quintet, 1H), 3.91 (q, 2H), 4.43 (s, 2H), 7.17 (t,d, 1H), 7.70-7.87 (m, 2H); MS: [M+H]= 305.

The following Examples were similarly prepared as described above for Example 1, by reductive alkylation of 1,1-dimethylethyl (3*S*)-3-(cyclobutylamino)pyrrolidine-1-carboxylate with the appropriate substituted benzaldehyde:

Example 40

(3*S*)-*N*-Cyclobutyl-*N*-{[5-fluoro-2-(trifluoromethyl)-phenyl]methyl}-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.41-2.04 (m, 8H), 2.82-2.89 (m, 1H), 2.98-3.07 (m, 1H), 3.16-3.30 (m, 2H), 3.33-3.43 (m, 1H), 3.51-3.62 (m, 1H), 3.71-3.92 (m, 4H), 7.24-7.31 (td, 1H), 7.66-7.79 (m, 2H); MS: [M+H] = 317.

Example 41

(3*S*)-*N*-Cyclobutyl-*N*-[(2,3-dichlorophenyl)methyl]-pyrrolidin-3-amine *L*-tartrate

MS: [M+H] = 299/301/303.

The following Examples were similarly prepared as described above for Example 1, by reductive alkylation of 1,1-dimethylethyl (3*S*)-3-(cyclohexylamino)pyrrolidine-1-carboxylate with the appropriate substituted benzaldehyde:

Example 42

(3*S*)-*N*-Cyclohexyl-*N*-[(3-methylphenyl)methyl]-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 0.99-1.39 (m, 5H), 1.51-1.54 (m, 1H), 1.60-1.78 (m, 5H), 1.91-1.97 (m, 1H), 2.28 (s, 3H), 2.36-2.42 (m, 1H), 2.77-2.83 (m, 1H), 2.97-3.06 (m, 1H), 3.14-3.24 (m, 2H), 3.59-3.71 (m, 3H), 3.96 (s, 2H), 6.99-7.02 (m, 1H), 7.12-7.21 (m, 3H); MS: [M+H] = 300.

Example 43

(3*S*)-*N*-Cyclohexyl-*N*-{[2-(methylthio)phenyl]methyl}-pyrrolidin-3-amine di-*D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 0.90-1.28 (m, 5H), 1.51-1.54 (m, 1H), 1.62-1.84 (m, 5H), 1.87-2.02 (m, 1H), 2.30-2.47 (m, 4H), 2.84-2.90 (m, 1H), 2.96-3.10 (m, 1H), 3.13-3.28 (m, 2H), 3.63-3.82 (m, 3H), 4.10 (s, 4H), 7.11-7.17 (m, 1H), 7.24 (d, 2H), 7.49 (d, 1H); MS: [M+H] = 305.

Example 44

(3*S*)-*N*-Cyclohexyl-*N*-{[2-(trifluoromethyl)phenyl]methyl}-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 0.95-1.27 (m, 5H), 1.52 (d, 1H), 1.59-1.78 (m, 5H), 1.90-2.03 (m, 1H), 2.38 (t, 1H), 2.83 (t, 1H), 2.96-3.10 (m, 1H), 3.15-3.27 (m, 2H), 3.66-3.90 (m, 5H), 7.43 (t, 1H), 7.61-7.70 (m, 2H), 7.91 (d, 1H); MS: [M+H] = 327.

Example 45

(3*S*)-*N*-Cyclohexyl-*N*-{[3-(trifluoromethylthio)phenyl]-methyl}-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 0.95-1.35 (m, 5H), 1.521-1.54 (m, 1H), 1.60-1.80 (m, 5H), 1.89-2.02 (m, 1H), 2.33-2.40 (m, 1H), 2.79-2.83 (m, 1H), 2.96-3.10 (m, 1H), 3.15-3.28 (m, 2H), 3.65-3.85 (m, 3H), 4.00 (s, 2H), 7.44-7.60 (m, 3H), 7.69 (s, 1H); MS: [M+H] = 359.

Example 46

(3*S*)-*N*-Cyclohexyl-*N*-[(2,4-dichlorophenyl)methyl]-pyrrolidin-3-amine di-*D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.05-1.25 (m, 5H), 1.51-1.55 (m, 1H), 1.62-1.77 (m, 5H), 1.90-2.02 (m, 1H), 2.32-2.45 (m, 1H), 2.80-2.86 (m, 1H), 2.96-3.09 (m, 1H), 3.15-3.29 (m, 2H), 3.68-3.82 (m, 3H), 4.09 (s, 4H), 7.42 (dd, 1H), 7.56 (d, 1H), 7.62 (d, 1H); MS: [M+H] = 327/329.

Example 47

(3*S*)-*N*-Cyclohexyl-*N*-[(3,5-dichlorophenyl)methyl]-pyrrolidin-3-amine sesqui-*D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.05-1.25 (m, 5H), 1.51-1.55 (m, 1H), 1.60-1.76 (m, 5H), 1.89-2.03 (m, 1H), 2.34-2.46 (m, 1H), 2.76-2.83 (m, 1H), 2.95-3.09 (m, 1H), 3.15-3.27 (m, 2H), 3.61-3.75 (m, 3H), 4.03 (s, 3H), 7.36-7.37 (m, 2H), 7.40-7.45 (m, 1H); MS: [M+H] = 327/329/331.

Example 48

(3*S*)-*N*-Cyclohexyl-*N*-[(2,3-dichlorophenyl)methyl]-pyrrolidin-3-amine *L*-tartrate

MS: [M+H] = 327/329/331.

The following Examples were similarly prepared as described above for Example 1, by reductive alkylation of 1,1-dimethylethyl (3*S*)-3-(2-methoxy-1-methylethyl amino)pyrrolidine-1-carboxylate with the appropriate substituted benzaldehyde:

Example 49

(3*S*)- *N*-[(2,4-Dichlorophenyl)methyl]-*N*-(2-methoxy-1-methylethyl)pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 0.98 (t, 3H), 1.59-1.77 (m, 1H), 1.86-2.04 (m, 1H), 2.75-3.07 (m, 3H), 3.10-3.38 (m, 7H), 3.65-3.90 (m, 5H), 3.43 (dd, 1H), 7.53-7.58 (m, 1H), 7.65 (dd, 1H); MS: [M+H] = 327/329/331.

Example 50

(3*S*)- *N*-[(2-Chloro-4-fluorophenyl)methyl]-*N*-(2-methoxy-1-methylethyl)pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 0.98 (t, 3H), 1.61-1.79 (m, 1H), 1.85-2.04 (m, 1H), 2.77-3.06 (m, 3H), 3.10-3.39 (m, 7H), 3.65-3.93 (m, 5H), 7.22 (td, 1H), 7.38 (dd, 1H), 7.60-7.39 (m, 1H); MS: [M+H] = 301.

Example 51

(3*S*)- *N*-[(3,5-Dichlorophenyl)methyl]-*N*-(2-methoxy-1-methylethyl)pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 0.90-1.00 (m, 3H), 1.57-1.75 (m, 1H), 1.85-2.03 (m, 1H), 2.73-3.07 (m, 3H), 3.10-3.37 (m, 7H), 3.59-3.94 (m, 5H), 7.41 (dd, 3H); MS: [M+H] = 317/319.

Example 52

(3*S*)- *N*-[(2,3-Dichlorophenyl)methyl]-*N*-(2-methylpropyl)-pyrrolidin-3-amine *L*-tartrate

To a solution of 1,1-dimethylethyl (3*S*)-3-(2-methylpropyl)-pyrrolidine-1-carboxylate (0.363g, 1.5mmol) in 1,2-dichloroethane (10mL) was added 2,3-dichlorobenzaldehyde (1.05 g, 6.0mmol), followed by sodium triacetoxyborohydride (0.95g, 4.5mmol), and the mixture left to stir for 16h. The reaction mixture was quenched with water (5 mL) and 2N sodium hydroxide (5 mL), and the organic layer separated by passing through a hydrophobic frit. The organic solution was diluted with methanol (5 mL) and absorbed onto an Isolute™ SCX-2 ion exchange cartridge (5 g), washed with methanol (15 mL) and the product eluted with 2M ammonia in methanol solution (15 mL). The solvent was removed *in vacuo* to give 1,1-dimethylethyl (3*S*)-3-{[(2,3-dichlorophenyl)methyl](2-methylpropyl)amino}pyrrolidine-1-carboxylate as a colourless oil. This was taken up in dichloromethane (2mL), trifluoroacetic acid (1.4mL, 18.3mmol) added, and the mixture stirred at room temperature for 16h. The solvent was removed *in vacuo* and the residue diluted with methanol (5 mL) and absorbeded onto an Isolute™ SCX-2 ion exchange cartridge (5 g). The column was washed with methanol (15 mL) and the product eluted with 2M ammonia in methanol solution (15 mL). The solvent was removed *in vacuo* and the residue purified by mass guided preparative LCMS. The residue was diluted with methanol (5 mL) and again absorbed onto an Isolute™ SCX-2 ion exchange cartridge (5 g). The column was washed with methanol (15 mL), the product eluted with 2M ammonia in methanol solution (15 mL) and the solvent removed *in vacuo*. The desired compound product was taken up in cyclohexane (15 mL) and a hot solution of *L*-tartaric acid (1 equiv.) in isopropanol (1 mL) was added. The solvent was removed *in vacuo* and the residue taken up in 40% acetonitrile/water and freeze dried to give the tile compound as a white solid.

^{1}H NMR δ_H (300 MHz, CD_3OD): 7.43 (1H, dd), 7.34 (1H, dd), 7.19 (1H, t), 4.28 (2H, s), 3.78-3.67 (2H, s), 3.60-3.49 (1H, m), 3.33-3.26 (2H, m), 3.15-2.97 (2H, m), 2.31-2.19 (2H, m), 2.07-1.97 (1H, m), 1.92-1.78 (1H, m), 1.54 (1H, septet), 0.76 (6H, d); MS: [M+1] = 301/303/305.

Example 53

(3*S*)-*N*-{[2-Chloro-4-fluorophenyl]methyl}-*N*-(1-methylethyl)pyrrolidin-3-amine *L*-tartrate

a) 1,1-Dimethylethyl (3*S*)-3-((1-methylethyl)-{[2-chloro-4-fluorophenyl]methyl}amino)pyrrolidine-1-carboxylate

To a solution of 1,1-dimethylethyl (3*S*)-3-[(1-methylethyl)amino]-pyrrolidine-1-carboxylate (0.5g, 2.19 mmol) and 2-chloro-4-fluorobenzaldehyde (1.23g, 4.38 mmol) in dichloroethane (15 mL) at room temperature under a nitrogen atmosphere was added portionwise sodium triacetoxyborohydride (1.16g, 5.48mmol). The reaction was stirred at room temperature for 72 hours. After this time analysis showed that some starting material was still present so an additional equivalent of the benzaldehyde and sodium triacetoxyborohydride was added, and the reaction stirred overnight. Starting material was still evident therefore a further equivalent of both benzaldehyde and sodium triacetoxyborohydride was added, together with DMF (2mL). After 16h all remaining starting material had disappeared. The reaction was evaporated to dryness *in vacuo*. The resulting residue was dissolved in methanol and absorbed onto a cationic ion exchange resin (Isolute ™ SCX-2). The basic components were recovered from the column by elution with 7N ammonia in methanol. This solution was concentrated *in vacuo* to yield the desired compound as an oil. This was used directly in the next step without further purification.

b) (3*S*)-*N*-{[2-Chloro-4-fluorophenyl]methyl}-*N*-(1-methylethyl)pyrrolidin-3-amine *L*-tartrate

1,1-Dimethylethyl (3*S*)-3-((1-methylethyl)-{[2-chloro-4-fluorophenyl]methyl}amino)pyrrolidine-1-carboxylate (0.81g, 2.19 mmol) was dissolved in a mixture of dichloromethane and trifluoroacetic acid (15 mL, 1:1) and stirred at room temperature for 2h. The reaction solution was concentrated *in vacuo* and re-dissolved in MeOH. This solution was absorbed onto a cationic ion exchange resin (Isolute ™ SCX-2). The basic components were isolated by elution with 7N ammonia in methanol and evaporated *in vacuo*. The residue was dissolved in hot isohexane (5 mL) and to this was added an equimolar amount of L-tartaric acid, dissolved in a minimal amount of hot isopropanol. The solution was evaporated *in vacuo* to yield the title compound as a solid.

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.59-7.54 (m, 1H), 7.09-7.00 (m, 1H), 6.99-6.94 (m, 1H), 4.29 (s, 2H), 3.74-3.63 (m, 3H), 3.19-3.06 (m, 1H), 2.94-2.85 (m, 2H), 2.05-1.95 (m, 1H), 1.84-1.71 (m, 1H), 0.98 (d, 3H), 0.96 (d, 3H), MS: [M+H] = 271.

The following Examples were similarly prepared from 1,1-dimethylethyl (3*S*)-3-[(1-methylethyl)amino]-pyrrolidine-1-carboxylate, by reductive alkylation with the appropriately substituted benzaldehyde and subsequent deprotection, as described above for Example 53:

Example 54

(3*S*)-*N*-{[4-Fluoro-2-(trifluoromethyl)phenyl]methyl}-*N*-(1-methylethyl)-pyrrolidin-3-amine *L*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 8.04-7.99 (m, 1H), 7.44-7.36 (m, 2H), 4.40 (s, 2H), 3.87 (s, 2H), 3.82-3.74 (m, 1H), 3.37-3.36 (m, 2H), 3.31-3.18 (m, 1H), 3.05-2.96 (m, 2H), 2.14-2.09 (m, 1H), 1.94-1.80 (m, 1H), 1.0 (m, 6H); MS: [M+H]=305.

Example 55

(3*S*)-*N*-{[2-Fluoro-4-(trifluoromethyl)phenyl]methyl}-*N*-(1-methylethyl)-pyrrolidin-3-amine *L*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.77-7.66 (m, 1H), 7.39-7.37 (m, 1H), 7.30-7.26 (m, 1H), 4.29 (s, 2H), 3.74 (s, 2H), 3.72-3.64 (m, 1H), 3.30-3.22 (m, 2H), 3.19-3.07 (m, 1H), 2.97-2.86 (m, 2H), 2.06-2.00 (m, 1H), 1.99-1.72 (m, 1H), 0.98 (m, 6H); MS: [M+H] = 305.

Example 56

(3*S*)-*N*-[(3,4-Dichlorophenyl)methyl]-*N*-(1-methylethyl)-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 1.10 (d, 3H), 1.10 (d, 3H), 1.80-1.94 (m, 1H), 2.07-2.15 (m, 1H), 2.93-3.06 (m, 2H), 3.15-3.39 (m, 3H), 3.66-3.80 (m, 3H), 6.70 (s, 2H), 7.32 (d,d, 1H), 7.47(d, 1H), 7.56 (d, 1H); MS: [M+H] = 287/ 289/291.

Example 57

(3*S*)-*N*-[(3,5-Dichlorophenyl)methyl]-*N*-(1-methylethyl)-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 1.08 (d, 3H), 1.11 (d, 3H), 1.79-1.93 (m, 1H), 2.08-2.18 (m, 1H), 2.93-3.05 (m, 2H), 3.16-3.25 (m, 1H), 3.30-3.40 (m, 2H), 3.67-3.81 (m, 3H), 6.70 (s, 2H), 7.30 (t, 1H), 7.37 (m, 2H); MS: [M+H] = 287/289/291.

Example 58

(3*S*)-*N*-[(4-Chlorophenyl)methyl]-*N*-(1-methylethyl)-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 1.08 (d, 3H), 1.10 (d, 3H), 1.83-1.96 (m, 1H), 2.06-2.14 (m, 1H), 2.92-3.06 (m, 2H), 3.15-3.38 (m, 3H), 3.64-3.79 (m, 3H), 6.70 (s, 2H), 7.30-7.39 (m, 4H); MS: [M+H] = 253/255.

Example 59

(3*S*)-*N*-[(3-Methoxyphenyl)methyl]-*N*-(1-methylethyl)-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 1.08 (d, 3H), 1.10 (d, 3H), 1.83-1.96 (m, 1H), 2.06-2.14 (m, 1H), 2.92-3.06 (m, 2H), 3.15-3.38 (m, 3H), 3.64-3.79 (m, 3H), 6.70 (s, 2H), 7.30-7.39 (m, 4H); MS: [M+H] = 249.

Example 60

(3*S*)-*N*-[(3-Cyano-4-fluorophenyl)methyl]-*N*-(1-methylethyl)-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 1.08 (d, 3H), 1.10 (d, 3H), 1.80-1.94 (m, 1H), 2.08-2.12 (m, 1H), 2.94-3.06 (m, 2H), 3.16-3.26 (m, 1H), 3.31-3.40 (m, 2H), 3.71-3.82 (m, 3H), 6.69 (s, 2H), 7.30-7.35 (m, 1H), 7.72-7.78 (m, 2H); MS: [M+H] = 262.

Example 61

(3*S*)-*N*-[(2,3-Dimethylphenyl)methyl]-*N*-(1-methylethyl)-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR: see Example 7 for data on fumarate; MS: [M+H] = 247.

Example 62

(3*S*)-*N*-{[(2-Chloro-3-(trifluoromethyl)phenyl]methyl}-*N*-(1-methylethyl)-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 0.97-1.01 (m, 6H), 1.60-1.74 (m, 1H), 1.92-2.02 (m, 1H), 2.82-2.93 (m, 2H), 2.98-3.08 (m, 1H), 3.19-3.27 (m, 2H), 3.65-3.79 (m, 1H), 3.82 (s, 2H), 3.93 (s, 2H), 7.54-7.59 (m, 1H), 7.73-7.75 (m, 1H), 7.94-7.96 (m, 1H). MS: [M+H] = 321/323.

Example 63

(3*S*)-*N*-[(2-Chloro-6-fluorophenyl)methyl]-*N*-(1-methylethyl)-pyrrolidin-3-amine *D*-tartrate

MS: [M+H] = 271/273.

Example 64

(3*S*)-*N*-[(2,4-Chlorophenyl)methyl]-*N*-(1-methylethyl)-pyrrolidin-3-amine *L*-tartrate

^{1}H NMR: see Example 8 for data on *L*-tartrate; MS: [M+H] = 287/289/291.

Example 65

(3*S*)-*N*-{[2-(4-Fluorophenoxy)phenyl]methyl}-*N*-(1-methylethyl)-pyrrolidin-3-amine *L*-tartrate

MS: [M+H] = 329.

Example 66

(3*S*)-*N*-{[2-(3,4-Difluorophenoxy)phenyl]methyl}-*N*-(1-methylethyl)-pyrrolidin-3-amine *L*-tartrate

MS: [M+H] = 347.

Example 67

(3*S*)-*N*-{(4'-Fluoro-[1,1'-biphenyl]-2-yl)methyl}-*N*-(1-methylethyl)-pyrrolidin-3-amine *L*-tartrate

MS: [M+H] = 313.

The following Examples were prepared by reductive alkylation of the appropriately substituted 1,1-dimethylethyl (3*S*)-3-(benzylamino)pyrrolidine-1-carboxylate (see Preparation above) with the appropriate aldehyde and subsequent deprotection, as described for Example 52:

Example 68

(3*S*)-*N*-{[4-Fluoro-2-(trifluoromethyl)phenyl]methyl}-*N*-propylpyrrolidin-3-amine *L*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.98-7.93 (m, 1H), 7.46-7.36 (m, 2H), 4.88(s, 1H), 3.92-3.79 (q, 2H), 3.79-3.58(quin, 1H), 3.45-3.33 (m, 2H), 3.31-3.20 (m, 1H), 3.14-3.07 (m, 1H), 2.57-2.52 (q, 2H), 2.20-2.12 (m, 1H), 1.99-1.89 (m, 1H), 1.55-1.42 (quin, 2H), 0.90-0.85 (t, 3H); MS: [M+H] = 305.

Example 69

(3*S*)-*N*-Butyl-*N*-{[4-fluoro-2-(trifluoromethyl)phenyl]-methyl}pyrrolidin-3-amine *L*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.98-7.93 (m, 1H), 7.46-7.36 (m, 2H), 4.88(s, 1H), 3.92-3.79 (q, 2H), 3.79-3.58(quin, 1H), 3.45-3.38 (m, 2H), 3.31-3.20 (m, 1H), 3.14-

3.07 (m, 1H), 2.61-2.56 (q, 2H), 2.20-2.12 (m, 1H), 2.09-1.89 (m, 1H), 1.50-1.40 (m, 2H), 1.36-1.24 (m, 2H), 0.91-0.86 (t, 3H); MS: [M+H] = 319.

Example 70

(3*S*)-*N*-Cyclopropylmethyl-*N*-{[4-fluoro-2-(trifluoromethyl)phenyl]-methyl}pyrrolidin-3-amine *L*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.95-7.90 (d, 1m), 7.36-7.27 (m, 2H), 4.32 (s, 2H), 3.94-3.85 (q, 2H), 3.80-3.67 (quin, 1H), 3.37-3.27 (m, 2H), 3.23-3.14 (m, 1H), 3.05-3.01(m, 1H), 2.40(d, 2H), 2.11-2.06 (m, 1H), 1.93-1.83 (m, 1H), 0.80-0.78 (m, 1H), 0.40-0.37(d, 2H), 0.01-0.003 (d, 2H); MS: [M+H] = 317.

Example 71

(3*S*)-*N*-[(3,5-Dichlorophenyl)methyl]-*N*-propylpyrrolidin-3-amine *L*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.24-7.21 (m, 3H), 4.76(s, 1H), 3.65-3.50 (m, 3H), 3.34-3.26 (m, 2H), 3.19-3.12 (m, 1H), 3.10-2.95 (m, 1H), 2.43-2.38 (q, 2H), 2.07-2.01 (m, 1H), 1.89-1.79 (m, 1H), 1.42-1.32 (m, 2H), 0.79-0.74 (t, 3H); MS: [M+H] = 287.

Example 72

(3*S*)-*N*-Butyl-*N*-[(3,5-dichlorophenyl)methyl]pyrrolidin-3-amine *L*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.24-7.21 (m, 3H), 4.76 (s, 1H), 3.65-3.51 (m, 3H), 3.48-3.27 (m, 2H), 3.20-3.12 (m, 1H), 3.08-2.95 (m, 1H), 2.46-2.42 (q, 2H), 2.07-1.99 (m, 1H), 1.87-1.76 (m, 1H), 1.39-1.30 (m, 2H), 1.25-1.18 (m, 2H), 0.87-0.78 (t, 3H); MS: [M+H] = 301/303/305.

Example 73

(3*S*)-*N*-Cyclopropylmethyl-*N*-[(3,5-dichlorophenyl)-methyl]pyrrolidin-3-amine *L*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.29 (s, 2H), 7.23 (s, 1H), 4.32 (s, 2H), 3.78-3.63 (m, 3H), 3.38-3.21 (m, 2H), 3.18-3.11 (m, 1H), 3.11-3.0 (m, 1H), 2.37 (d, 2H), 2.13-2.08 (m, 1H), 1.94-1.84 (m, 1H), 0.80-0.77 (m, 1H), 0.43-0.40 (d, 2H), 0.03 (d, 2H); MS: [M+H] = 299.

Example 74

(3S)-N-[(2,4-Dichlorophenyl)methyl]-N-propylpyrrolidin-3-amine L-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.45 (d, 1H, J= 8.29Hz), 7.32 (d, 1H, J= 2.26Hz), 7.25 (dd, 1H, J= 2.07Hz, 6.22Hz, 2.07Hz), 4.76 (s, 2H), 3.74-3.61 (q, 2H), 3.59-3.48 (quin, 1H), 3.34-3.22 (m, 2H), 3.18-3.11 (m, 1H), 3.09-2.98 (m, 1H), 2.45-2.40 (m, 2H), 2.10-2.00 (m, 1H), 1.92-1.79 (m, 1H), 1.43-1.31 (m, 2H), 0.77-0.72 (m, 3H); MS: [M+H] = 287/289/291.

Example 75

(3*S*)-*N*-Butyl-*N*-[(2,4-dichlorophenyl)methyl]pyrrolidin-3-amine *L*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.46 (d, 1H), 7.33 (d, 1H), 7.23 (dd, 1H), 4.30 (s, 2H), 3.74-3.61 (q, 2H), 3.56-3.48 (quin, 1H), 3.3-3.27 (m, 2H), 3.16-3.09 (m, 1H), 3.05-2.98 (m, 1H), 2.49-2.44 (m, 2H), 2.08-1.92 (m, 1H), 1.89-1.79 (m, 1H), 1.38-1.28 (m, 2H), 1.23-1.05 (m, 2H), 0.79-0.74 (m, 3H); MS: [M+H] = 301/303/305.

Example 76

(3*S*)-*N*-Cyclopropylmethyl-*N*-[(2,4-dichlorophenyl)-methyl]pyrrolidin-3-amine *L*-tartrate

^{1}H NMR (300 MHz, CD_3OD) $\square_H$: 7.58 (d, 1H), 7.35 (d, 1H), 7.25 (dd, 1H), 4.32 (s, 2H), 3.88-3.67(m, 3H), 3.38-3.28 (m, 2H), 3.22-3.12 (m, 1H), 3.08-3.02 (m, 1H), 2.40 (d,

2H), 2.14-2.06 (m, 1H), 1.96-1.86 (m, 1H), 0.81-0.77 (m, 1H), 0.39 (d, 2H), 0.01-0.002 (d, 2H); MS: [M+H] = 299.

Example 77

(3*S*)-*N*-[(2-Chloro-4-fluorophenyl)methyl]-*N*-propylpyrrolidin-3-amine *L*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.51-7.46 (m, 1H), 7.11-7.00 (m, 1H), 6.98-6.94 (m, 1H), 4.77 (s, 2H), 3.74-3.59 (q, 2H), 3.59-3.48 (quin, 1H), 3.33-3.27 (m, 2H), 3.18-3.09 (m, 1H), 3.06-2.99 (m, 1H), 2.45-2.40 (m, 2H), 2.08-2.00 (m, 1H), 1.93-1.80 (m, 1H), 1.43-1.31 (m, 2H), 0.86-0.72 (m, 3H); MS: [M+H] = 271.

Example 78

(3*S*)-*N*-Butyl-*N*-[(2-chloro-4-fluorophenyl)methyl]-pyrrolidin-3-amine *L*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.51-7.46 (m, 1H), 7.11-7.00 (m, 1H), 6.98-6.94 (m, 1H), 4.76 (s, 2H), 3.74-3.60 (q, 2H), 3.56-3.51 (quin, 1H), 3.32-3.26 (m, 2H), 3.16-3.09 (m, 1H), 3.06-2.99 (m, 1H), 2.48-2.43 (m, 2H), 2.09-2.03 (m, 1H), 1.94-1.83 (m, 1H), 1.39-1.29 (m, 2H), 1.23-1.13 (m, 2H), 0.79-0.74 (m, 3H); MS: [M+H] = 285.

Example 79

(3*S*)- *N*-[(2-Chloro-4-fluorophenyl)methyl]-*N*-(cyclopropylmethyl)pyrrolidin-3-amine *L*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.60-7.55 (m, 1H), 7.13-7.09 (m, 1H), 7.03-6.96 (m 1H), 4.33 (s, 2H), 3.87-3.67(m, 3H), 3.38-3.28 (m, 2H), 3.22-3.15 (m, 1H), 3.09-3.03 (m, 1H), 2.39 (d, 2H), 2.14-2.08 (m, 1H), 1.90-1.87 (m, 1H), 0.80-0.72 (m, 1H), 0.40 (d, 2H), 0.011-0.002 (d, 2H); MS: [M+H] = 283.

Example 80

(3*S*)-*N*-{[4-Fluoro-2-(trifluoromethyl)phenyl]methyl}-*N*-(tetrahydro-2*H*-thiopyran-4-yl)pyrrolidin-3-amine *L*-tartrate

a) 1,1-Dimethylethyl (3*S*)-3-[(tetrahydro-2*H*-thio-pyran-4-yl)amino]pyrrolidine-1-carboxylate

Neat tetrahydro-4*H*-thiopyran-4-one (4.2g, 36mmol) and 1,1-dimethylethyl (3*S*)-3-aminopyrrolidine-1-carboxylate (6.73g, 36mmol) were stirred together in ethanol for 16h Sodium borohydride (2.74g, 72mmol) was added portionwise. The reaction was then quenched with water and the solvent removed *in vacuo*. The residue was dissolved in water and the solution extracted with dichloromethane. The combined organics were dried (Na_2SO_4), filtered and evaporated *in vacuo* to provide the title compound as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.69-3.48 (m, 3H), 3.46-3.31 (m, 1H), 2.98-2.80 (m, 1H), 2.75-2.74 (m, 1H), 2.67-2.64 (m, 3H), 2.58-2.50 (m, 1H), 2.46-2.20 (m, 3H), 2.19-2.14 (m, 1H), 1.77-1.65 (m, 2H), 1.56-1.48 (m, 2H), 1.45 (s, 9H).

b) (3*S*)-*N*-{[4-Fluoro-2-(trifluoromethyl)phenyl]methyl}-*N*-(tetrahydro-2*H*-thiopyran-4-yl)pyrrolidin-3-amine *L*-tartrate

1,1-Dimethylethyl (3*S*)-3-[(tetrahydro-2*H*-thio-pyran-4-yl)amino]pyrrolidine-1-carboxylate was reductively alkylated with 4-fluoro-2-(trifluoromethyl)benzaldehyde and deprotected, as described above for Example 52.

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.99-7.94 (m, 1H), 7.46-7.36 (m, 2H), 4.40 (s, 2H), 3.94-3.81 (m, 3H), 3.42-3.21 (m, 3H), 3.19-2.97 (m, 1H), 2.50-2.49 (m, 5H), 2.28-2.20 (m, 3H), 1.97-1.90 (m, 1H), 1.75-1.62 (m, 2H); MS: [M+H] = 363.

Example 81

(3*S*)-*N*-[(2,4-Dichlorophenyl)methyl]-*N*-(tetrahydro-2*H*-thiopyran-4-yl)pyrrolidin-3-amine *L*-tartrate

Prepared as described above for Example 80.

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.50 (d, 1H), 7.33 (d, 1H), 7.23 (dd, 1H), 4.32 (s, 2H), 3.82-3.77 (m, 2H), 3.26-3.10 (m, 2H), 2.93-2.86 (m, 1H), 2.56-2.53 (m, 4H), 2.38-2.34 (m, 1H), 2.09-1.99 (m, 3H), 1.83-1.80 (m, 1H), 1.59-1.53 (m, 2H), MS: [M+H] = 345/347/349.

Example 82

(3*S*)-*N*-[(2,4-Dichlorophenyl)methyl]-*N*-(1,1-dioxido-tetrahydro-2*H*-thiopyran-4-yl)pyrrolidin-3-amine *L*-tartrate

a) 1,1-Dimethylethyl (3*S*)-3-[[(2,4-dichlorophenyl)-methyl](1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)amino]pyrrolidine-1-carboxylate

To a ice cold solution of 1,1-dimethylethyl (3*S*)-3-[[(2,4-dichlorophenyl)-methyl](2*H*-thiopyran-4-yl)-amino]pyrrolidine-1-carboxylate (0.675g, 1.5mmol) in ethyl acetate (5mL) was added dropwise peracetic acid solution (35% in acetic acid) (0.77mL, 3.7mmol) and left to stir for 30 min. The reaction mixture was absorbed onto a cationic ion exchange resin (Isolute ™ SCX-2). The basic components were recovered from the column by elution with 7N ammonia in methanol. The eluate was concentrated *in vacuo* and the resultant product taken onto the next step without further purification.

b) (3*S*)-*N*-[(2,4-Dichlorophenyl)methyl]-*N*-(1,1-dioxido-tetrahydro-2*H*-thiopyran-4-yl)pyrrolidin-3-amine *L*-tartrate

1,1-Dimethylethyl (3*S*)-3-[[(2,4-dichlorophenyl)-methyl](1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)amino]pyrrolidine-1-carboxylate was deprotected in trifluoroacetic acid/dichloromethane (1:1) and purified, as described above in Example 54.

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.50-7.49 (m, 1H), 7.42-7.40 (m, 1H), 7.26-7.23 (m, 1H), 4.27 (s, 2H), 3.86-3.72 (m, 1H), 3.35-2.97 (m, 5H), 2.94-2.90 (m, 2H), 2.82-2.75 (m, 1H), 2.30-2.21 (m, 2H), 2.06-1.98 (m, 4H), 1.85-1.82 (m, 1H); MS: [M+H] = 377/379/381.

Example 83

(3*S*)-*N*-{[5-Fluoro-2-(trifluoromethyl)phenyl]methyl}-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolidin-3-amine *D*-tartrate

a) 1,1-Dimethylethyl (3*S*)-3-[(tetrahydro-2*H*-pyran-4-yl)amino]pyrrolidine-1-carboxylate

Neat tetrahydro-4*H*-pyran-4-one (18.7g, 100mmol) and 1,1-dimethylethyl (3*S*)-3-aminopyrrolidine-1-carboxylate (26.1g, 140.1 mmol) were stirred together for 20 minutes prior to addition of anhydrous dichloroethane (140mL). The solution was then cooled to 0°C under nitrogen and stirred as sodium triacetoxyborohydride (59.2g, 281mmol) was added portionwise. The reaction was allowed to warm to room temperature and stirred for 5 days, after which the reaction solution was carefully poured onto ice-cold aqueous sodium hydrogen carbonate solution. The phases were separated and the aqueous phase washed with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by automated flash chromatography on silica, eluting with methanol in ethyl acetate (0:100 to 30:70), to provide the title compound as an off-white solid.

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.13-1.29 (m, 2H), 1.39 (s, 9H), 1.55-1.65 (m, 1H), 1.68-1.81 (m, 2H), 1.87-2.00 (m, 1H), 2.64 (sep, 1H), 2.91 (sex, 1H), 3.10-3.45 (m, 6H), 3.81 (dt, 2H). MS: [M+H] = 271, [M+H-tBu] = 215.

b) (3*S*)-*N*-{[5-Fluoro-2-(trifluoromethyl)phenyl]methyl}-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolidin-3-amine *D*-tartrate

To a stirred solution of 1,1-dimethylethyl (3*S*)-3-[(tetrahydro-2*H*-pyran-4-yl)amino]pyrrolidine-1-carboxylate (1.12g, 4.2mmol) and 5-fluoro-2-(trifluoromethyl)benzaldehyde (4.56g, 23.8mmol) in anhydrous dichloroethane (50mL) was added portionwise sodium triacetoxyborohydride (3.86g, 18.3mmol). The reaction mixture was stirred at room temperature under nitrogen and the reaction progress was followed by MS. After 2 days more reagents were added: 5-fluoro-2-(trifluoromethyl)benzaldehyde (0.98g, 5.1mmol) and sodium triacetoxyborohydride (3.00g, 14.2mmol), and after a further 2 days the reaction was found to be complete. The reaction solution was carefully poured onto ice-cold saturated aqueous sodium hydrogen carbonate solution and filtered through a PTFE hydrophobic frit. The organic phase was concentrated *in vacuo* and the residue redissolved in methanol. The methanolic solution was filtered through a cationic ion exchange resin (Isolute ™ SCX-2) and the basic components isolated by elution with 2N ammonia in methanol. After concentrating *in vacuo,* the residue was redissolved in dichloromethane /trifluoro-acetic acid (2:1) and allowed to stir at room temperature for 4 hours. The reaction mixture was concentrated *in vacuo* and redissolved in methanol. The methanolic solution was filtered through a cationic ion exchange resin (Isolute ™ SCX-2) and the basic components isolated by elution with 2N ammonia in methanol. The crude product was purified by UV guided prep-LC, and the desired compound collected from the acidic prep-LC mobile phase *via* a cationic ion exchange resin, as described above. The basic product was dissolved in hot cyclohexane and to this was added an equimolar amount of *D*-tartaric acid dissolved in a minimal amount of hot isopropanol. The solution was allowed to cool overnight, and the next day the resultant solid was filtered off and dried *in vacuo*, to yield the title compound as a white crystalline solid.

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.40-1.80 (m, 5H), 1.91-2.06 (m, 1H), 2.61-2.74 (m, 1H), 2.81-2.93 (dd, 1H), 2.97-3.11 (dt, 1H), 3.12-3.31 (m, 4H), 3.69-3.96 (m, 7H), 7.49-7.61 (m, 2H), 7.90-7.99 (m, 1H). MS: [M+H] = 347.

The following Examples were similarly prepared from 1,1-dimethylethyl (3*S*)-3-[(tetrahydro-2*H*-pyran-4-yl)amino]pyrrolidine-1-carboxylate and the appropriate benzaldehyde, as described above for Example 83:

Example 84

(3*S*)-*N*-{[2-(Trifluoromethyl)phenyl]methyl}-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolidin-3-amine hemi-*D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.35-1.75 (m, 5H), 1.90-2.04 (m,1H), 2.63-2.75 (m, 1H), 2.76-2.86 (m, 1H), 2.94-3.03 (m, 1H), 3.10-3.25 (m, 4H), 3.67-3.90 (m, 6H), 7.43 (t, 1H), 7.66 (t, 2H), 7.92 (d, 1H); MS: [M+H] = 329.

Example 85

(3*S*)-*N*-[(2,4-Dichlorophenyl)methyl]-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.35-1.75 (m, 5H), 1.91-2.04 (m, 1H), 2.62-2.75 (m, 1H), 2.78-2.85 (m, 1H), 2.91-3.04 (m, 1H), 3.13-3.27 (m, 4H), 3.67-3.90 (m, 7H), 7.42 (dd, 1H), 7.52-7.58 (m, 1H), 7.63 (d, 1H); MS: [M+H] = 329/331.

Example 86

(3*S*)-*N*-[(3,5-Dichlorophenyl)methyl]-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolidin-3-amine di-*D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.35-1.75 (m, 5H), 1.93-2.06 (m, 1H), 2.63-2.76 (m, 1H), 2.79-2.86 (m,1H), 2.96-3.09 (m, 1H), 3.15-3.30 (m, 4H), 3.64-3.90 (m, 5H), 4.04 (s, 4H), 7.37 (m, 2H), 7.43-7.44 (m, 1H); MS: [M+H] = 329/331.

Example 87

(3*S*)-*N*-[(2-Chloro-4-fluorophenyl)methyl]-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.35-1.77 (m, 5H), 1.92-2.05 (m, 1H), 2.60-2.75 (m, 1H), 2.81-2.88 (m, 1H), 2.95-3.08 (m, 1H), 3.19-3.29 (m, 4H), 3.68-3.90 (m, 7H), 7.18-7.25 (m, 1H), 7.38-7.41 (m, 1H), 7.60-7.65 (m, 1H); MS: [M+H] = 313/315.

Example 88

(3*S*)-*N*-[(4-Chloro-2-methylphenyl)methyl]-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolidin-3-amine sesqui-*D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.40-1.81 (m, 5H), 1.89-2.03 (m, 1H), 2.28 (s, 3H), 2.59-2.74 (m, 1H), 2.82-2.88 (m, 1H), 2.94-3.07 (m, 1H), 3.12-3.29 (m, 4H), 3.62-3.90 (m, 5H), 3.98 (s, 3H), 7.16-7.24 (m, 2H), 7.42-7.50 (m, 1H); MS: [M+H] = 309/311.

Example 89

(3*S*)-*N*-[(2,3-Dichlorophenyl)methyl]-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolidin-3-amine *L*-tartrate

^{1}H NMR δ_H (300 MHz, CD_3OD): 7.53 (1H, dd), 7.32 (1H, dd), 7.19 (1H, t), 4.32 (2H, s), 3.88-3.80 (5H, m), 3.31-3.20 (4H, m) 3.17-3.07 (1H, m), 2.95-2.88 (1H, m), 2.78-2.67 (1H, m), 2.09-1.98 (1H, m), 1.88-1.72 (1H, m), 1.66-1.44 (4H, m); MS: [M+1] = 329.

Example 90

(3*S*)-*N*-[(2-Chloro-6-fluorophenyl)methyl]-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolidin-3-amine *D*-tartrate

MS: [M+H] = 313/315.

Example 91

(3*S*)-*N*-{[5-Fluoro-2-(trifluoromethyl)phenyl]methyl}-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolidin-3-amine *L*-tartrate

^{1}H NMR: see Example 83 for data of *D*-tartrate; MS: [M+H] = 347.

Example 92

(3*S*)-*N*-{[4-Fluoro-2-(trifluoromethyl)phenyl]methyl}-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.40-1.80 (m, 5H), 1.91-2.06 (m, 1H), 2.61-2.74 (m, 1H), 2.81-2.93 (m, 1H), 2.97-3.11 (m, 1H), 3.12-3.31 (m, 4H), 3.69-3.96 (m, 7H), 7.49-7.61 (m, 2H), 7.90-7.99 (m, 1H). MS: [M+H] = 347.

Example 93

(3*S*)-*N*-([1,1'-Biphenyl]-2-ylmethyl)-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolidin-3-amine *L*-tartrate

MS: [M+H] = 337.

Example 94

(3*S*)-*N*-{(4-Fluoro-[1,1'-biphenyl]-2-yl)methyl}-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolidin-3-amine *L*-tartrate

MS: [M+H] = 355.

Example 95

(3*S*)-*N*-[(2-Chlorophenyl)methyl]-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolidin-3-amine *L*-tartrate

MS: [M+H] = 295/297.

Example 96

(3*S*)-*N*-[(2-Chloro-5-fluorophenyl)methyl]-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolidin-3-amine *L*-tartrate

MS: [M+H] = 313/315.

Example 97

(3*S*)-*N*-[(4-Fluorophenyl)methyl]-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrrolidin-3-amine *L*-tartrate

MS: [M+H] = 279.

Example 98

(3*S*)-*N*-(1-Methylethyl)-*N*-{[2-(trifluoromethyl)-5-fluorophenyl]methyl}pyrrolidin-3-amine fumarate

a) 1,1-Dimethylethyl (3*S*)-3-((1-methylethyl)-{[2-(trifluoromethyl)-5-fluorophenyl]methyl}amino)-pyrrolidine-1-carboxylate

A solution of 1,1-dimethylethyl (3*S*)-3-[(1-methylethyl)amino]pyrrolidine-1-carboxylate (0.34g, 1.5mmol) and 2-(trifluoromethyl)-5-fluorobenzyl bromide (0.58g, 2.25mmol) in acetonitrile (5mL) was heated at reflux with anhydrous potassium carbonate (0.41g, 3mmol) for 24 hours. The reaction mixture was cooled, diluted with ethyl acetate and washed with water. The organic extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated *in vacuo* to give an oil. This was purified by flash

chromatography on silica, eluting with ethyl acetate/cyclohexane (0:100 to 10:90), to give the title compound as an oil.

b) (3*S*)-*N*-(1-Methylethyl)-*N*-{[2-(trifluoromethyl)-5-fluorophenyl]methyl}pyrrolidin-3-amine fumarate

A solution of 1,1-dimethylethyl (3*S*)-3-((1-methylethyl)-{[2-(trifluoromethyl)-5-fluorophenyl]-methyl}amino)-pyrrolidine-1-carboxylate (0.26g) in a mixture of trifluoroacetic acid (2mL), dichloromethane (8mL) and water (0.2mL) was stirred at room temperature for 3 hours. The reaction mixture was evaporated *in vacuo*. The crude mixture was taken up in methanol and absorbed onto an SCX-2 ion exchange cartridge. After initially washing with methanol, the product was eluted with 2M methanolic ammonia and the collected fractions evaporated *in vacuo*. The crude product was taken up in methanol and fumaric acid (1 equiv.) in methanol added. The solvent was removed *in vacuo* and the resultant gum triturated with diethyl ether. The solid formed was filtered off and dried *in vacuo* at 50°C to yield the title compound as an off-white microcrystalline solid.

^{1}H NMR (300 MHz, CD_3OD) δ_H: 1.09 (d, 3H), 1.10 (d, 3H), 1.87 (m, 1H), 2.15 (m, 1H), 3.01 (m, 2H), 3.23 (m, 1H), 3.38 (m, 2H), 3.81 (m, 1H), 3.91 (s, 2H), 6.70 (s, 2H), 7.15 (dt, 1H), 7.73 (m, 2H); MS: [M+H] = 305.

The following Examples were similarly prepared as described for Example 98, using the appropriate substituted benzyl bromide in step b) above:

Example 99

(3*S*)-*N*-(1-Methylethyl)-*N*-{[3-(trifluoromethyl)phenyl]-methyl}pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 1.10 (d, 3H), 1.11 (d, 3H), 1.89 (m, 1H), 2.13 (m, 1H), 3.00 (m, 2H), 3.21 (m, 1H), 3.36 (m, 2H), 3.78 (m, 1H), 3.82 (s, 2H), 6.70 (s, 2H), 7.48-7.54 (m, 2H), 7.63-7.71 (m, 2H); MS: [M+H] = 287.

Example 100

(3*S*)-*N*-(1-Methylethyl)-*N*-{[4-(trifluoromethyl)phenyl]-methyl}pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 1.10 (d, 3H), 1.11 (d, 3H), 1.89 (m, 1H), 2.12 (m, 1H), 3.00 (m, 2H), 3.20 (m, 1H), 3.33 (m, 2H), 3.77 (m, 1H), 3.81 (s, 2H), 6.70 (s, 2H), 7.58 (d, 2H), 7.62 (d, 2H); MS: [M+H] = 287.

Example 101

(3*S*)-*N*-([1,1'-Biphenyl]-2-ylmethyl)-*N*-(1-methylethyl)-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 0.95 (d, 6H), 1.75 (m, 1H), 1.91 (m, 1H), 2.75 (dd, 1H), 2.93 (sept, 1H), 3.10 (m, 2H), 3.25 (m, 1H), 3.60 (m, 3H), 6.70 (s, 2H), 7.17 (dd, 1H), 7.25-7.48 (m, 7H), 7.67 (d, 1H); MS: [M+H]= 295.

Example 102

(3*S*)-*N*-(1-Methylethyl)-*N*-{[2-phenyloxy)phenyl]methyl}-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 1.03 (d, 3H), 1.04 (d, 3H), 1.87-2.11 (m, 2H), 2.99-3.09 (m, 2H), 3.14-3.37 (m, 3H), 3.56-3.81 (m, 3H), 6.70 (s, 2H), 6.86-6.93 (m, 3H), 7.08(t, 1H), 7.15-7.28 (m, 2H), 7.31-7.38 (m, 2H), 7.62 (dd, 1H); MS: [M+H]= 311.

Example 103

(3*S*)-*N*-(1-Methylethyl)-*N*-{[2-(phenylmethyl)phenyl]-methyl}pyrrolidin-3-amine fumarate

MS: [M+H]= 309.

Example 104

(3*S*)-*N*-[[(2,4-Dichlorophenyl)methyl]-*N*-(2,2,2-trifluoroethyl)amino]pyrrolidin-3-amine *D*-tartrate

a) 1,1-Dimethylethyl (3*S*)-3-{[(2,4-dichloro-phenyl)methyl]amino}pyrrolidine-1-carboxylate

A solution of 2,4-dichlorobenzaldehyde (4.67g, 26 mmol) and 1,1-dimethylethyl (3*S*)-3-aminopyrrolidine-1-carboxylate (5g, 26mmol) in dry methanol (104mL) under nitrogen atmosphere, was stirred at room temperature for 14 hours. The aldimine in methanol was carefully treated with solid sodium borohydride (1.58g, 41.6 mmol). The reaction mixture was stirred for 10 minutes, then quenched with an saturated aqueous solution of sodium hydrogen carbonate (50mL). Volatiles were removed *in vacuo*, and the residue taken up in a mixture of water and dichloromethane (100mL, 1:1). The phases were separated and the aqueous layer further extracted with dichloromethane (3x 50mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to dryness *in vacuo*. The resulting yellow oil was used in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.45 (s, 9H), 1.66-1.76 (m, 1H), 1.98-2.09 (m, 1H), 3.07-3.21 (m, 1H), 3.28-3.58 (m, 4H), 3.84 (s, 2H), 7.20-7.27 (m, 1H), 7.32-7.37 (m, 2H). MS: [M+H] = 345/347/349 (3:2).

b) 1,1-Dimethylethyl (3*S*)-3-[[(2,4-dichlorophenyl)-methyl](trifluoroacetyl)amino]pyrrolidine-1-carboxylate

To a solution of 1,1-dimethylethyl (3*S*)-3-{[(2,4-dichloro-phenyl)methyl]amino}pyrrolidine-1-carboxylate (2g, 5.8mmol) in dry dichloromethane (33mL) under nitrogen was added successively triethylamine (1.61mL, 11.6mmol), trifluoroacetic anhydride (0.99mL, 6.95mmol) and *N,N*-dimethyl-4-aminopyridine (0.35g, 2.9mmol). The resulting mixture was stirred at room temperature for 30 minutes, then quenched with a saturated aqueous solution of sodium hydrogen carbonate (20mL). The two phases were separated and the aqueous phase further extracted with dichloromethane (3x 20mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica, eluting with ethyl acetate in *n*-heptane (0:100 to 50:50). This yielded the title compound as a colourless oil.

MS: [M+Na] = 463/465/467.

c) 1,1-Dimethylethyl (3*S*)-3-[[(2,4-dichlorophenyl)-methyl](2,2,2-trifluoroethyl)amino]pyrrolidine-1-carboxylate

Neat borane-dimethylsulfide complex (1.31mL, 16.3mmol) was added dropwise to an ice-cold solution of 1,1-dimethylethyl (3*S*)-3-[[(2,4-dichlorophenyl)-methyl]-(trifluoroacetyl)amino]pyrrolidine-1-carboxylate (2.4g, 5.44mmol) in dry tetrahydrofuran (50mL) under nitrogen. The resulting solution was then heated under reflux for 3 hours. After cooling to room temperature the reaction was carefully poured into a saturated aqueous solution of sodium hydrogen carbonate (200mL). The suspension was extracted with dichloromethane (3x 200mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The resulting residue was purified by flash chromatography on silica, eluting with ethyl acetate in *n*-heptane (0:100 to 50:50), to yield the title compound as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.44 (s, 9H), 1.72-1.86 (m, 1H), 1.99-2.08 (m, 1H), 3.09-3.23 (m, 4H), 3.42-3.60 (m, 3H), 3.95 (s, 2H), 7.23-7.28 (m, 1H), 7.35-7.37 (m, 1H), 7.43-7.48 (m, 1H).

d) (3*S*)-*N*-[[(2,4-Dichlorophenyl)methyl]-*N*-(2,2,2-trifluoroethyl)amino]pyrrolidin-3-amine *D*-tartrate

1,1-Dimethylethyl (3*S*)-3-[[(2,4-dichlorophenyl)-methyl](2,2,2-trifluoroethyl)amino]pyrrolidine-1-carboxylate (1.4g, 3.3mmol) was dissolved in a mixture of dichloromethane and trifluoroacetic acid (10mL, 2:1), and stirred at room temperature for 30 minutes. The reaction mixture was then concentrated *in vacuo* and redissolved in methanol. This solution was filtered through a cationic ion exchange resin (Isolute ™ SCX-2) and the basic fractions isolated by elution with 2N ammonia in methanol. After evaporation *in vacuo* the residue (1.09g) was dissolved in hot cyclohexane (5mL) and to this was added an equimolar quantity of *D*-tartaric acid (0.49g) dissolved in a minimal amount of hot isopropanol. The solution was evaporated *in vacuo* to yield the title compound as a solid.

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.68-1.81 (m, 1H), 2.01-2.11 (m, 1H), 2.90-3.05 (m, 2H), 3.23-3.33 (m, 2H), 3.42-3.63 (m, 3H), 3.92-3.93 (m, 4H), 7.44-7.47 (m, 1H), 7.52-7.55 (m, 1H), 7.59-7.60 (m, 1H). MS: [M+H]= 327/329/331.

The following Examples were similarly prepared as described above for Example 104:

Example 105

(3*S*)-*N*-[[(3,5-Dichlorophenyl)methyl]-*N*-(2,2,2-trifluoroethyl)amino]pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.65-1.79 (m, 1H), 2.00-2.10 (m, 1H), 2.87-3.05 (m, 2H), 3.23-3.32 (m, 2H), 3.42-3.61 (m, 3H), 3.86 (s, 2H), 3.95 (s, 2H), 7.37-7.38 (m, 2H), 7.50-7.51 (m, 1H). MS: [M+H] = 327/329/331.

Example 106

(3*S*)-*N*-[{[2-(Trifluoromethyl)phenyl]methyl}-*N*-(2,2,2-trifluoroethyl)amino]pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.66-1.80 (m, 1H), 1.98-2.06 (m, 1H), 2.88-3.03 (m, 2H), 3.21-3.27 (m, 2H), 3.49-3.57 (m, 3H), 3.88 (s, 2H), 4.04 (s, 2H), 7.46-7.51 (m, 1H), 7.68-7.73 (m, 2H), 7.79-7.81 (m, 1H). MS: [M+H]= 327.

Example 107

(3*S*)-*N*-[[(2,3-Dichlorophenyl)methyl]-*N*-(2,2,2-trifluoroethyl)amino]pyrrolidin-3-amine *L*-tartrate

MS: [M+H]= 327/329/331.

Example 108

(3*S*)-*N*-[[(2-Chloro-3-methylphenyl)methyl]-*N*-(2,2,2-trifluoroethyl)amino]pyrrolidin-3-amine *L*-tartrate

MS: [M+H]= 307/309.

Example 109

Methyl ((3*S*)-pyrrolidin-3-yl{[2-(trifluoromethyl)phenyl]-methyl}amino)acetate *D*-tartrate

60% Sodium hydride oil dispersion (39mg, 0.95mmol) was added to 1,1-dimethylethyl (3*S*)-3-({[2-(trifluoromethyl)-phenyl]methyl}amino)pyrrolidine-1-carboxylate (250mg, 0.73mmol) in DMF (5mL). After heating at 50°C for 1 hour under nitrogen, methyl bromoacetate (123mg, 0.73mmol) was added. After heating overnight at

50°C overnight, excess water was added and the product was extracted into ether. The ether was washed with water, dried ($MgSO_4$) and evaporated *in vacuo* to give an oil (460mg). The oil was dissolved in dichloromethane (5mL) and trifluoroacetic acid (0.5mL) was added. After stirring for 1 day, the solution was evaporated *in vacuo* to give an oil. The oil was purified using preparative LCMS to give the product as the acetate salt, which was converted to the free base by absorption onto a cationic ion exchange resin (Isolute ™ SCX-2) and eluting the basic fractions with 2N ammonia in methanol. The resultant oil was converted to the *D*-tartaric acid salt (crystallised from ethanol/ diethyl ether) to give the title compound as a white solid.

^{1}H NMR(300 MHz, CD_3OD) δ_H: 1.84-196 (m, 1H), 2.06-2.14 (m, 1H), 3.06-3.37 (2 x m,6H), 3.57 (s, 3H), 3.77-3.86 quin,1H), 3.91-4.06 (q, 2H), 4.29 (s, 2H), 7.32-7.36 (t, 1H), 7.49-7.54 (t, 1H), 7.56-7.59 (d, 1H), 7.76-7.89 (d, 1H); MS: [M+H] = 317.

The following Examples were prepared from 1,1-dimethylethyl (3*S*)-3-aminopyrrolidine-1-carboxylate by initial reductive alkylation with 2-methylpropanaldehyde as described above for Example 104 a), followed by a second reductive alkylation with the appropriate benzaldehyde and subsequent deprotection as described above for Example 52.

Example 110

(3*S*)-*N*-[(2-Chlorophenyl)methyl]-*N*-(2-methylpropyl)-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) $\square_H$: 0.77-0.80 (dd, 6H), 1.52-1.66 (sep, 1H), 1.82-1.95 (m, 1H), 1.20-2.10 (m, 1H), 2.20-2.32 (m, 2H), 2.99-3.16 (m, 2H), 3.26-3.35 (m, 2H), 3.56 (quin, 1H), 3.70-3.77 (m, 2H), 6.60 (s, 2H), 7.13-7.24 (m, 2H), 7.29 (dd, 1H), 7.46 (dd,1H); MS: [M+H] = 267.

Example 111

(3*S*)-*N*-{[2-(Methoxy)phenyl]methyl}-*N*-(2-methylpropyl)pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 0.82 (dd, 6H), 1.66 (sept, 1H), 1.79-1.92 (m, 1H), 1.92-2.06 (m, 1H), 2.19-2.22 (m, 2H), 2.96-3.13 (m, 2H), 3.18-3.31 (m, 2H), 3.59-3.67 (m, 2H), 3.74 (s, 3H), 6.59 (s, 2H), 6.80-6.87 (m, 2H), 7.11-7.18 (m, 1H), 7.25 (dd, 1H); MS: [M+H] = 263.

Example 112

(3*S*)-*N*-{[2-(Ethyloxy)phenyl]methyl}-*N*-(2-methylpropyl)pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) □$_H$: 0.73-0.76 (2x d, 6H), 1.27-1.32 (t, 3H), 1.56-1.70 (sep, 1H), 1.76-1.89 (m, 1H), 1.92-2.02 (m, 1H), 2.17 (dd, 1H), 2.92-3.07 (m, 2H), 3.07-3.19 (m, 2H), 3.47-3.63 (m, 3H), 3.89-3.96 (m, 2H), 6.55 (s, 2H), 6.74-6.81 (m, 2H), 7.08 (dt, 1H), 7.21 (dd, 1H); MS: [M+H] = 277.

Example 113

(3*S*)-*N*-[(2-Methylphenyl)methyl]-*N*-(2-methylpropyl)-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.78-7.36 (m, 1H), 7.12-7.13 (m, 3H), 6.65 (s,2H), 3.51-3.72b(q+m, 3H), 3.24-3.42 (m, 2H+MeOH), 3.01-3.19 (m, 2H), 2.34 (s, 3H), 2.26-2.29 (dd, 2H), 1.91-2.13 (m,2H), 1.55-1.69 sep, 1H), 0.81-0.84 (d, 6H); MS: [M+H] = 247.

Example 114

(3*S*)-*N*-(2-Methylpropyl)-*N*-(phenylmethyl)pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.36-7.49 (m, 5H), 6.84 (s, 2H), 3.70-3.91 (q+quin, 3H), 3.28-3.56 (m, 2H), 3.16-3.24 (m, 1H), 2.45-2.47 (dd, 2H), 2.20-2.31 (m, 1H), 2.05-2.16 (m, 1H), 1.85-1.99 (sep, 1H), 1.05-1.07 (d, 6H); MS: [M+H] = 233.

Example 115

(3*S*)-*N*-(2-Methylpropyl)-*N*-[(naphthalen-1-yl)methyl]-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 8.37-8.40 (m, 1H), 7.90-7.99 (M, 2H), 7.51-7.70 (m, 4H), 6.79 (s, 2H), 4.16-4.33 (q, 2H), 3.70-3.81 (quin, 1H), 3.36-3.53 (m, 2H), 3.18-3.31 (m, 2H), 2.49-2.54 (d, 2H), 2.06-2.27 (m, 2H), 1.78-1.87 (m, 1H), 0.96-0.99 (d, 6H); MS: [M+H] = 283.

Example 116

(3*S*)-*N*-{[4-Fluoro-2-(methoxy)phenyl]methyl}-*N*-(2-methylpropyl)pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.08-7-12 (d, 1H), 6.84-6.93 (m,3H), 6.63 (s, 2H), 3.76 (s, 3H), 3.48-3.68 (m, 3H), 3.25-3.36 (m, 2H), 2.99-3.18 (m, 2H), 2.20-2.32 (dd, 2H), 2.01-2.11 (m, 1H) 1.81-1.95 (m, 1H), 1.61-1.75 (sep, 1H, 0.82-86 (dd, 3H); MS: [M+H] = 281.

Example 117

(3*S*)-*N*-(2-Methylpropyl)-*N*-{[2-(phenyloxy)phenyl]methyl}-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.51-7.54 (dd, 1H), 7.04-7.35 (m, 5H), 6.86-6.91 (m, 3H), 6.67 (s, 2H), 3.62-3.76 (m, 3H), 3.24-3.36 (m, 2H), 3.00-3.18 (m, 2H), 2.27-2.30 (dd, 2H), 1.96-2.06 (m, 1H), 1.86-1.93 (m, 1H), 1.68-1.76 (quin, 1H), 0.84-0.87 (dd, 6H); MS: [M+H] = 325.

Example 118

(3*S*)-*N*-{[2-Chloro-3-(trifluoromethyl)phenyl]methyl}-*N*-(2-methylpropyl)pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.77 (1H, s), 7.46-7.39 (2H, m), 4.24 (2H, s), 3.72 (2H, m), 3.66-2.92 (5H, m), 2.25-2.15 (2H, m), 2.08-1.96 (1H, m), 1.88-1.73 (1H, m), 1.57-1.43 (1H, m), 0.73 (6H, dd); MS: [M+H] = 335.

Example 119

(3*S*)-*N*-[(2-Chloro-4-fluorophenyl)methyl]-*N*-(2-methylpropyl)pyrrolidin-3-amine di-*D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 0.76-0.80 (m, 6H), 1.50-1.66 (m, 1H), 1.70-1.86 (m, 1H), 1.92-2.05 (m, 1H), 2.18-2.30 (m, 2H), 2.90-3.11 (m, 2H), 3.20-3.32 (m, 2H), 3.45-3.56 (m, 1H), 3.60-3.72 (m, 2H), 4.12 (s, 4H), 7.23 (td, 1H), 7.41 (dd, 1H), 7.57 (dd, 1H); MS: [M+H] = 285 and 287.

Example 120

(3*S*)-*N*-[(2,4-Dichlorophenyl)methyl]-*N*-(2-methylpropyl)-pyrrolidin-3-amine sesqui-*D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 0.77-0.80 (m, 6H), 1.51-1.65 (m, 1H), 1.69-1.86 (m, 1H), 1.92-2.06 (m, 1H), 2.24-2.26 (m, 2H), 2.90-3.10 (m, 2H), 3.20-3.32 (m, 2H), 3.43-3.58 (m, 1H), 3.62-3.68 (m, 2H), 4.05 (s, 3H), 7.44 (dd, 1H), 7.50-7.59 (m, 2H); MS: [M+H] = 301/303/305.

Example 121

(3*R*)-*N*-{[2-Chloro-3-(trifluoromethyl)phenyl]methyl}-*N*-(2-methylpropyl)pyrrolidin-3-amine *D*-tartrate

^{1}H NMR: Spectra were comparable with the *S* enantiomer as described in Example 118; MS: [M+H] = 335.

Example 122

(3*R*)-*N*-[(2-Chloro-3-methylphenyl)methyl]-*N*-(2-methylpropyl)pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.44-7.39 (1H, m), 7.22-7.17 (2H, m), 4.40 (2H, s), 3.87-3.76 (2H, d), 3.71-3.08 (5H, m), 2.25-2.15 (2H, m), 2.08-1.96 (1H, m), 1.88-1.73 (1H, m), 1.57-1.43 (1H, m), 0.73 (6H, dd); MS: [M+H] = 335/337.

Example 123

(3*R*)-*N*-[(2-Chloro-4-fluorophenyl)methyl]-*N*-(2-methylpropyl)pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.42-7.37 (1H, dd), 7.04 (1H, dd), 7.02 (1H, dd), 6.90 (1H, dt), 4.21 (2H, s), 3.57 (2H, m), 3.51-3.40 (1H, m), 3.25-2.89 (4H, m), 2.21-2.09 (2H, dd), 2.00-1.89 (1H, m), 1.85-1.71 (1H, m), 1.55-1.41 (1H, m), 0.69-0.66 (6H, dd); MS: [M+H] = 285/287.

Example 124

(3*S*)-*N*-{[3-Fluoro-2-(trifluoromethyl)phenyl]methyl}-*N*-(2-methylpropyl)pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.97-7.93 (1H, dd), 7.46-7.37 (2H, m), 4.41 (2H, s), 3.84 (2H, s), 3.68-3.57 (1H, m), 3.45-3.36 (1H, m), 3.34-3.32 (1H, m), 3.26-3.17 (1H, m), 3.12-3.01 (1H, m), 2.42-2.31 (2H, m), 2.16-2.05 (1H, m), 2.01-1.88 (1H, m), 1.76-1.62 (1H, m), 0.91 (6H, dd); MS: [M+H] = 319.

Example 125

(3*R*)-*N*-{[4-Fluoro-2-(trifluoromethyl)phenyl]methyl}-*N*-(2-methylpropyl)pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.73 (1H, d), 7.67-7.59 (1H, m), 7.25-7.19 (1H, m) 4.41 (2H, s), 3.91 (2H, m), 3.65-3.55 (1H, m), 3.45-3.35 (1H, m), 3.34-3.32 (1H, m), 3.26-3.16 (1H, m), 3.11-3.04 (1H, m), 2.40-2.33 (2H, m), 2.18-2.07 (1H, m), 2.01-1.90 (1H, m), 1.96-1.56 (1H, m), 0.90 (6H, dd); MS: [M+H] = 319.

Example 126

(3*S*)-*N*-(2-Methylpropyl)-*N*-{[2-(methylthio)phenyl]methyl}-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.44 (1H, d), 7.32 (2H, m), 7.17 (1H, dt), 4.41 (2H, s), 3.81-3.60 (2H, m), 3.44-3.32 (4H, m), 3.25-3.14 (1H, m), 2.47 (1H, S), 2.32 (2H, dd), 2.18-1.94 (2H, m), 1.71-1.60 (1H, m), 1.73 (6H, dd); MS: [M+H] = 279.

Example 127

(3*R*)-*N*-(2-Methylpropyl)-*N*-{[2-(methylthio)phenyl]methyl}-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR: Spectra were comparable with the *S* enantiomer as described in Example 126; MS: [M+H] = 279.

Example 128

(3*S*)-*N*-[(2-Chloro-3-methylphenyl)methyl]-*N*-(2-methylpropyl)-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 0.79-0.81 (m, 6H), 1.53-1.64 (m, 1H), 1.70-1.84 (m, 1H), 1.87-2.12 (m, 1H), 2.26-2.28 (m, 2H), 2.33 (s, 3H), 2.90-3.07 (m, 2H), 3.21-3.28

(m, 2H), 3.45-3.56 (m, 1H), 3.69-3.70 (m, 2H), 3.88 (s, 2H), 7.20-7.26 (m, 2H), 7.38-7.41 (m, 1H). MS: [M+H] = 281/283.

Example 129

(3*S*)-*N*-[(3,5-Dichlorophenyl)methyl]-*N*-(2-methylpropyl)-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 0.80-0.82 (m, 6H), 1.58-1.79 (m, 2H), 1.92-2.02 (m, 1H), 2.15-2.27 (m, 2H), 2.87-2.94 (m, 1H), 2.98-3.07 (m, 1H), 3.22-3.29 (m, 2H), 3.43-3.54 (m, 1H), 3.56-3.69 (m, 2H), 3.94 (s, 2H), 7.36-7.37 (m, 2H), 7.46-7.47 (m, 1H). MS: [M+H] = 301/303/305.

Example 130

(3*S*)-*N*-[(3-Chloro-2-methylphenyl)methyl]-*N*-(2-methylpropyl)-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 0.77-0.79 (m, 6H), 1.49-1.63 (m, 1H), 1.71-1.85 (m, 1H), 1.91-2.01 (m, 1H), 2.21-2.23 (m, 2H), 2.34 (s, 3H), 2.89-3.06 (m, 2H), 3.19-3.29 (m, 2H), 3.39-3.50 (m, 1H), 3.56-3.69 (m, 2H), 3.87 (bs, 2H), 7.16-7.21 (m, 1H), 7.32-7.35 (m, 2H). MS: [M+H] = 281/283.

The following Examples were prepared from 1,1-dimethylethyl (3*S*)-3-({[2-(trifluoromethyl)phenyl]-methyl}amino)pyrrolidine-1-carboxylate by reductive alkylation with the appropriate aldehyde or ketone and subsequent deprotection, as described above for Example 53.

Example 131

(3*S*)-*N*-(3,3-Dimethylbutyl)-*N*-{[2-(trifluoromethyl)-phenyl]methyl}pyrrolidin-3-amine sesquifumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.70-7.73 (d, 1H), 7.38-7.48 (d+t, 2H), 7.19-7.24 (t, 1H), 6.50 (s, 3H), 3.60-3-74 (q, 2H), 3.37-3.47 (quin, 1H), 2.87-3.30 (m, 6H), 2.39-2.45 (m, 2H), 1.91-2.02 (m, 1H), 1.70-1.83 (m, 1H); MS: [M+H] = 329.

Example 132

(3*S*)-*N*-(1-Methylethyl)-*N*-{[2-(trifluoromethyl)-phenyl]methyl}pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.98-8.00 (d, 1H), 7.60-7.68 (d+t, 2H), 7.38-7.43(t, 1H), 6.70 (s, 2H), 3.91 (bs, 2H), 3.74-3.85 (m, 1H), 3.17-3.40 (M, 5H), 2.96-3.10 (m,3H), 2.08-2.18 (m, 1H), 1.82-1.96 (m,1H), 1.08-1.11 (dd, 6H); MS: [M+H] = 287.

Example 133

(3*S*)-*N*-(2-methylpropyl)-*N*-{[2-(trifluoromethyl)phenyl]-methyl}pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.72-7.75 (t, 1H), 7.42-7.51 (d+t, 2H), 7.72-7.27 (t, 1H), 6.51 (s, 2H), 3.63-3.74 (bs, 2H), 3.38-3.49 (m, 1H), 2.86-3.25 (m, 2H), 2.17-2.25 (m, 2H), 1.88-1.99 (m,1H), 1.69-1.83 (m, 1H), 1.46-1.59 (m, 1H), 0.74-0.76 (d, 6H); MS: [M+H] = 301.

Example 134

(3*R*)-*N*-(2-Methylpropyl)-*N*-{[2-(trifluoromethyl)phenyl]-methyl}pyrrolidin-3-amine

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.92-7.94 (d, 1H), 7.60-7.69(d+t, 2H), 7.41-7.46 (t, 1H), 6.69 (s, 1H), 3.82-3.93 (bs, 2H), 3.56-3.68 (m,1H), 3.32-3.44 (m, 2H), 3.05-3.24 (m, 2H), 2.31-2.43 (dd, 2H), 2.07-2.17 (m,1H), 1.88-1.98 (m,1H), 1.65-1.78 (m, 1H), 0.92-0.95 (d, 6H); MS: [M+H] = 301.

Example 135

(3*S*)-*N*-Ethyl-*N*-{[2-(trifluoromethyl)phenyl]methyl}-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 8.00-8.03 (d, 1H), 7.67-7.76 (d+t, 2H), 7.47-7.52 (t, 1H), 6.77 (s, 2H), 3.89-4.03 (q, 2H), 3.65-3.75 (quin, 2H), 3.43-3.53 (m, 2H), 3.28-3.41 (m, 1H), 3.17-3.23 (m, 1H), 2.73-2.84 (q, 2H), 2.19-2.30 (m, 2H), 2.19-2.30 (m, 1H), 1.98-2.14 (m, 1H), 1.10-1.15 (t, 3H); MS: [M+H] = 273.

Example 136

(3*S*)-*N*-Propyl-*N*-{[2-(trifluoromethyl)phenyl]methyl}-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.92-7.94 (d, 1H), 7.60-7.69) d+t, 2H), 7.40-7.45 (t, 1H), 6.69-6.73 (s, 2H), 3.82-3.98 (q, 2H), 5.59-3.69(quin, 1H), 3.35-3.45 (m, 2H), 2.80-3.21 (m, 1H), 3.08-3.15 (m, 1H), 2.54-2.59 (q, 2H), 2.10-2.21 (m, 1H), 1.90-2.06 (m, 1H), 1.44-1.56 (quin, 2H), 0.86-0.91 (T, 3H); MS: [M+H] = 287.

Example 137

(3*S*)-*N*-(Cyclohexylmethyl)-*N*-{[2-(trifluoromethyl)-phenyl]methyl}pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 77.89-7.92 (d, 1H), 7.61-7.70 (d+t, 2H), 7.41-7.49 (t, 1H), 6.70 (s, 2H), 3.81-3.95 (q, 2H), 3.56-3.67 (quin, 1H), 3.31-3.43 (m, 2H), 3.14-3.23 (m, 1H), 3.04-3.11 (m, 1H), 2.39-2.41 (d, 2H), 2.06-2.13 (m, 1H), 1.70-2.01 (m, 6H), 1.34-1.46 (m, 1H), 1.12-1.23 (m, 1H), 0.83-0.89 (m, 2H); MS: [M+H] = 341.

Example 138

(3*S*)-*N*-(Cyclopropylmethyl)-*N*-{[2-(trifluoromethyl)-phenyl]methyl}pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.88-7.91 (d, 1H), 7.50-7.59 (d+t, 2H), 7.30-7.50 (t, 1H), 6.60 (s, 2H), 3.89-3.99 (q, 2H), 3.65-3.76 (quin, 1H), 3.27-3.35 (m, 2H), 3.10-3.22 (m, 1H), 2.99-3.06 (q, 1H), 2.40-2.43 (d, 2H), 2.04-2.15 (m, 1H), 1.81-1-95 (m, 1H), 0.73-0.85 (m, 1H), 0.34-0.42 (d, 2H), 0.02-0.05 (d, 2H); MS: [M+H] = 299.

Example 139

(3*S*)-*N*-(2-Phenylethyl)-*N*-{[2-(trifluoromethyl)phenyl]-methyl}pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.67-7.69 (d, 1H), 7.55-7.58 (d, 1H), 7.42-7.47 (t, 1H), 7.23-7.33 b(t, 1H), 7.01-7.17 (m, 5H), 6.58 (s, 2H), 3.80-3.93 (q, 2H), 3.47-3.64 (m, 1H), 3.20-3.40 (m, 2H), 3.07-3.18 (m, 1H), 2.91-2.98 (M, 1H), 2.71-2.76 (m, 2H), 2.62-2.67 (m,2H), 2.00-2.20 (m, 1H), 1.78-1.91 (m, 1H); MS: [M+H] = 349.

Example 140

(3*S*)-*N*-Butyl-*N*-{[2-(trifluoromethyl)phenyl]methyl}-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.91-7.94 (d, 1H), 7.60-7.69 (m, 2H), 7.40-7.45 (t, 1H), 6.70 (s, 2H), 3.82-3.96 (q, 2H), 3.59-3.69 (quin, 1H), 3.32-3.50 (m, 2H), 3.22-3.29 (m, 1H), 3.09-3.15 (q, 1H), 2.58-2.63 (t, 2H), 2.10-2.21 (m, 1H), 1.90-2.04 (m, 1H), 1.42-1.51 (m, 2H), 1.17-1.37 (m, 2H), 0.87-0.91 (t, 3H); MS: [M+H] = 301.

Example 141

(3*S*)-*N*-(2-Ethylbutyl)-*N*-{[2-(trifluoromethyl)phenyl]-methyl}pyrrolidin-3-amine sesquifumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.77-7.80 (d, 1H), 7.49-7.60 (m, 2H), 7.29-7.34 (t, 1H), 6.60 (s, 1.5H), 3.70-3.81 (q, 2H), 3.46-3.57 (quin, 1H), 3.20-3.33 (m, 2H), 2.94-3.13

(m, 2H), 2.32-2.34 (d, 2H), 1.97-2.07 (m 1H), 1.78-1.91 (m, 1H), 1.05-1.40 (m, 5H), 0.69-0.76 (m, 6H). MS: [M+H] = 329.

Example 142

(3*S*)-*N*-(2-Methylprop-2-enyl)-*N*-{[2-(trifluoromethyl)-phenyl]methyl}pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.78-7.81 (d, 1H), 7.49-7.58 (m, 2H), 7.29-7.34 (t, 1H), 6.57 (s, 2H), 4.80-4.91 (d, 2H), 3.68-3.80 (q, 2H), 3.52-3.62 (quin, 1H), 3.20-3.33 (m, 2H), 1.96-2.08 (m, 1H), 1.83-1.93 (m, 1H), 1.66 (s, 3H); MS: [M+H] = 299.

Example 143

(3*S*)-*N*-{[2-(Trifluoromethyl)phenyl]methyl}-*N*-(3,3,3-trifluoropropyl)pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.76-7.78 (d, 1H), 7.50-7.60 (d+t, 2H), 7.32-7.37 (t, 1H), 6.58 (s, 2H), 3.75-3.89 (q, 2H), 3.48-3.59 (quin, 1H), 3.126-3.22 (m, 1H), 2.98-3.05 (dd, 1H), 2.75-2.80 (t, 2H), 2.18-2.34 (m, 2H), 2.02-2.13 (m, 1H), 1.80-1.93 (m, 1H); MS: [M+H] = 341.

Example 144

(3*S*)-*N*-(4,4,4-Trifluorobutyl)-*N*-{[2-(trifluoromethyl)-phenyl]methyl}pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.75-7.77 (d, 1H), 7.50-7.59 (d+t, 2H), 7.31-7.40 (t, 1H), 1.65 (s, 2H), 3.73-7.86 (q, 2H), 3.48-3.59 (quin, 1H), 3.25-3.42 (m, 2H), 3.07-3.17 (m, 1H), 2.97-3.03 (m, 1H), 2.54-2.59 (t, H), 1.98-2.11 (m, 3H), 1.79-1.95 (m, 1H), 1.52-1.62 (quin, 2H); MS: [M+H] = 355.

Example 145

(3*S*)-*N*-(Furan-2-ylmethyl)-*N*-{[2-(trifluoromethyl)phenyl]-methyl}pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.83-7.86 (d, 1H), 7.49-7.58 (t+s, 2H), 7.29-7.38 (m, 2H), 6.23-6.26 (m, 1H), 6.14-6.15 (m, 1H), 4.30 (s, 2H), 3.78-3.91 (q, 2H), 3.66-3.67 (m, 2H), 3.25-3.55 (m, 3H), 2.30-3.17 (m, 2H), 2.05-2.16 (m, 1H), 1.83-1.96 (m, 1H); MS: [M+H] = 325.

Example 146

(3*S*)-*N*-(3-Methylbutyl)-*N*-{[2-(trifluoromethyl)phenyl]-methyl}pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.67-7.70 (d,1H), 7.35-7.45 (d+t, 2H), 7.1`6-7.21 (t, 1H), 4.16-4.18 (s, 2H), 3.57-3.71 (q, 2H), 3.35-3.45 (quin, 1H), 3.14-3.21 (m,2H), 2.97-3.04 (m, 1H), 2.84-2.91 (m,1H), 2.35-2.40 (m, 2H), 1.86-1.97 (m, 1H), 1.66-1.79 (m, 1H), 1.24-1.37 (sept, 1H), 1.08-1.16 (m, 2H), 0.59-0.62 (d, 6H); MS: [M+H] = 315.

Example 147

(3*S*)-*N*-[3-(Methylthio)propyl]-*N*-{[2-(trifluoromethyl)-phenyl]methyl}pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.90-7.92 (d,1H), 7.61-7.70 (d+t, 2H), 7.41-7.46 (t, 1H), 4.42 (s, 2H), 3.84-3.97 (q, 2H), 3.59-3.69 (quin, 1H), 3.38-3.47 (m, 2H), 3.19-3.29 (m, 1H), 3.09-3.16 (m, 1H), 2.70-2.77 (dt, 2H), 2.48-2.52 (t, 2H), 2.08-2.21 (m, 1H), 1.89-2.08 (s+m, 4H), 1.69-1.79 (quin, 2H); MS: [M+H] = 333.

Example 148

(3*S*)-*N*-(2,2-Dimethylpropyl)-*N*-{[2-(trifluoromethyl)-phenyl]methyl}pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 8.10-8.12 (d, 1H), 7.65-7.70 (t, 2H), 7.41-7.46 (t, 1H), 4.41 (s, 2H), 4.01 (s, 2H), 3.50-3.62 (quin, 1H), 3.31-3.43 (m, 2H), 3.04-3.20 (m, 2H), 2.50 (s, 2H), 2.06-2.17 (m, 1H), 1.85-1.99 (m, 1H), 0.96 (s, 9H): MS: [M+H] = 315.

Example 149

N-(Phenylmethyl)-*N*-[(3*S*)-pyrrolidin-3-yl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.93-7.96 (d, 1H), 7.60-7.68 (q, 2H), 7.23-7.44 (m, 6H), 6.69 (s, 2H), 3.83-3.94 (s,2H), 3.61-3.80 (m, 3H), 3.32-3.44 (m, 2H), 3.08-3.25 (m, 2H), 1.99-2.22 (m, 2H); MS: [M+H] = 335.

Example 150

(3*S*)-*N*-[(4-Fluorophenyl)methyl]-N-{[2-(trifluoromethyl)-phenyl]methyl}pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.90-8.00 (d, 1H), 7.59-7.67 (q, 2H), 7.31-7.44 (m, 3H), 7.02-7.08 (t, 2H), 6.71 (s, 2H), 3.88 (s, 2H), 3.56-3.77 (m, 3H), 3.31-3.52 (m, 2H), 3.15-3.26 (m, 2H), 1.99-2.22 (m, 2H); MS: [M+H] 353.

Example 151

(3*S*)-*N*-{[2-(Ethyloxy)phenyl]methyl}-*N*-{[2-(trifluoromethyl)phenyl]methyl}pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.84-7.87 (d, 1H), 7.52-7.64 (m, 2H), 7.18-7.39 (m, 3H), 6.85-6.96 (m, 2H), 6.70 (s, 2H), 4.06-4.13 (q, 2H), 3.95-3.97 (s,2H), 3.61-3.86 (m, 3H), 3.61-3.51 (m,4H), 2.04-2.20 (m,2H), 1.42-1.46 (t,3H); MS: [M+H] = 379.

Example 152

(3*S*)-*N*-[(2-Chlorophenyl)methyl]-*N*-{[2-(trifluoromethyl)-phenyl]methyl}pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.84-7.87 (d,1H), 7.62-7.64 (d, 1H), 7.50-7.57 (m,2H), 7.35-7.40 (m, 2H), 7.20-7.29 (m, 2H), 6.69 (s, 2H), 3.88-3.97 (m, 4H), 3.65-3.76 (quin, 1H), 3.38-3.47 (m, 2H), 3.18-3.28 (m, 2H), 2.05-2.26 (m, 2H); MS: [M+H] = 369.

Example 153

(3*S*)-*N*-[(2-Fluorophenyl)methyl]-*N*-{[2-(trifluoromethyl)-phenyl]methyl}pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.83-7.86 (d, 1H), 7.62-7.65 (d, 1H), 7.54-7.65 (t, 1H), 7.36-7.45 (m, 2H), 7.25-7.32 (m, 1H), 7.04-7.15 (m, 2H), 6.69 (s,2H), 3.92 (bs, 2H), 3.76-3.88 (q, 2H), 3.75-3.64 (quin, 21H), 3.37-3.46 (m, 2H), 3.18-3.27 (m, 2H), 2.01-2.24 (m, 2H); MS: [M+H] = 353.

Example 154

(3*S*)-*N*-{[2-(Methyloxy)phenyl]methyl}-*N*-{[2-(trifluoromethyl)phenyl]methyl}pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.85-7.87 (d, 1H), 7.61-7.64 (d, 1H), 7.52-7.58 (t, 1H), 7.21-7.40 (m, 3H), 6.81-6.97 (m, 2H), 6.69 (s, 2H), 3.61-3.97 (m, 8H), 3.16-3.44 (m, 4H), 1.20-2.21 (m, 2H); MS: [M+H] = 365.

Example 155

(3*S*)-*N*,*N*-bis{[2-(Trifluoromethyl)phenyl]methyl}-pyrrolidin-3-amine fumarate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.90-7.92 (d, 2H), 7.66-7.69 (d, 2H),7.59-7.64 (t, 2H), 7.40-7.45 (t, 2H), 6.69 (s, 2H), 3.91 (s, 4H), 3.62-3-74 (quin, 1H), 3.36-3.46 (m, 2H), 3.16-3.26 (m, 2H), 2.02-2.24 (m, 2H); MS: [M+H] = 403.

Example 156

(3*S*)-*N*-(2-Ethylbutyl)-*N*-{[2-(trifluoromethyl)-phenyl]methyl}pyrrolidin-3-amine, *D*-tartrate

^{1}H NMR (300MHz, CD_3OD): δ_H 7.94-7.92 (d, 1H), 7.72-7.69 (m, 2H), 7.48-7.43 (t, 1H), 4.44 (s, 2H), 3.96-3.84 (m, 2H), 3.71-3.60 (m, 1H), 3.46-3.38 (m, 2H), 3.28-3.18 (m, 1H), 3.15-3.08 (m, 1H), 2.49-2.47 (m, 2H), 2.20-2.10 (m, 1H), 2.05-1.91 (m, 1H), 1.54-1.24 (m, 5H), 0.90-0.83 (t, 6H); MS: [M+H] = 329.

Example 157

(3*S*)-*N*-{[2-(Trifluoromethyl)phenyl]methyl}-*N*-(3,3,3-trifluoropropyl)pyrrolidin-3-amine, *D*-tartrate

^{1}H NMR (300MHz, CD_3OD): δ_H 7.93-7.90 (d, 1H), 7.74-7.64 (m, 2H), 7.51-7.46 (t, 1H), 4.44 (s, 2H), 4.02-3.89 (m, 2H), 3.73-3.62 (m, 1H), 3.50-3.42 (m, 2H), 3.36-3.23 (m, 1H), 3.18-3.12 (dd, 1H), 2.94-2.89 (m, 2H), 2.48-2.32 (m, 2H), 2.24-2.15 (m, 1H), 2.07-1.94 (m, 1H); MS: [M+H] = 341.

Example 158

(3*S*)-*N*-(4,4,4-Trifluorobutyl)-*N*-{[2-(trifluoromethyl)-phenyl]methyl}pyrrolidin-3-amine, *D*-tartrate

^{1}H NMR (300MHz, CD_3OD): δ_H 7.92-7.89 (d, 1H), 7.73-7.64 (m, 2H), 7.50-7.45 (t, 1H), 4.44 (s, 2H), 4.00-3.87 (m, 2H), 3.73-3.63 (m, 1H), 3.49-3.41 (m, 2H), 3.32-3.25 (m, 1H), 3.22-3.11 (dd, 1H), 2.73-2.69 (m, 2H), 2.24-2.09 (m, 3H), 2.06-1.93 (m, 1H), 1.76-1.66 (m, 2H); MS: [M+H] = 355.

Example 159

(3*S*)-*N*-Ethyl-*N*-{[2-(trifluoromethyl)-phenyl]methyl}-pyrrolidin-3-amine, *D*-tartrate

MS: [M+H] = 273.

The following Examples were prepared from 1,1-dimethylethyl (3*S*)-3-aminopyrrolidine-1-carboxylate by reductive alkylation with two equivalents of the appropriate benzaldehyde and subsequent deprotection as described above for Example 53.

Example 160

(3*S*)-*N,N-bis*-[(2-Chloro-4-fluorophenyl)methyl]-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.83-2.13 (m, 2H), 3.00-3.17 (m, 2H), 3.22-3.36 (m, 2H), 3.51-3.59 (m, 1H), 3.68-3.78 (m, 4H), 3.87 (s, 2H), 7.14 (td, 2H), 7.34 (dd, 2H), 7.51 (dd, 2H); MS: [M+H] = 371/373.

Example 161

(3*S*)-*N,N-bis*-[(2,4-Dichlorophenyl)methyl]-pyrrolidin-3-amine *D*-tartrate

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.81-1.97 (m, 1H), 1.99-2.12 (m, 1H), 2.99-3.15 (m, 2H), 3.21-3.35 (m, 2H), 3.50-3.60 (m, 1H), 3.69-3.80 (m, 4H), 3.86 (s, 2H), 7.35 (dd, 2H), 7.48-7.52 (m, 4H); MS: [M+H] = 403/405/407.

Example 162

1-{[(3,5-Dichlorophenyl)methyl][(3*S*)-pyrrolidin-3-yl]amino}-2-methylpropan-2-ol *D*-tartrate

To a solution of 1,1-dimethylethyl (3*S*)-3-([(3,5-dichlorophenyl)methyl]amino)pyrrolidine-1-carboxylate (1.11g, 3.2mmol) in ethanol (30mL) was added isobutylene oxide (1mL, 11.2mmol) and water (10mL). The reaction mixture was heated to reflux. After 2 hours additional isobutylene oxide (5mL, 56.1mmol) was added, and a similar amount again after 3 days. After a total of 4 days at reflux no further reaction was observed (LC-MS), so the reaction was halted. The cooled reaction mixture was concentrated *in vacuo* and then redissolved in methanol. The crude product was absorbed onto a cationic ion exchange resin (Isolute ™ SCX-2) and the basic fraction recovered from the column by elution with 2N ammonia in methanol. The eluate was concentrated *in vacuo* and the residue redissolved in dichloromethane/ trifluoroacetic acid (2:1) and stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and redissolved in methanol, and again purified on a cationic ion exchange resin cartridge (Isolute ™ SCX-2). The recovered basic fractions were further purified by UV guided prep-LC and the desired compound collected from the acidic preparative-LC mobile phase *via* a cationic ion exchange resin as described above. The residue was dissolved in hot cyclohexane and to this was added an equimolar amount of *D*-tartaric acid dissolved in a minimal amount of hot isopropanol. The solution was allowed to crystallise overnight, and the resulting solid was filtered off and dried *in vacuo*, to yield the title compound as a white crystalline solid.

^{1}H NMR (300 MHz, d6-DMSO) δ_H: 1.07 (s, 6H), 1.65 (m, 1H), 1.90 (m, 1H), 2.40 (s, 2H), 2.78-2.99 (m, 2H), 3.14 (m, 2H), 3.46 (m, 1H), 3.72-3.90 (m, 4H), 7.46 (s, 3H). MS: [M+H] = 317/319/321.

The following Examples were similarly prepared as described above for Example 162:

Example 163

1-{[(2,4-Dichlorophenyl)methyl][(3*S*)-pyrrolidin-3-yl]amino}-2-methylpropan-2-ol *L*-tartrate

MS: [M+H] = 317/319/321.

Example 164

1-{{[4-Fluoro-2-(trifluoromethyl)phenyl]methyl}[(3*S*)-pyrrolidin-3-yl]amino}-2-methylpropan-2-ol *D*-tartrate

MS: [M+H] = 335.

Example 165

1-{[(2-Chloro-4-fluorophenyl)methyl][(3*S*)-pyrrolidin-3-yl]amino}-2-methylpropan-2-ol *D*-tartrate

MS: [M+H] = 301/303.

Example 166

1-{[(2-Chloro-6-fluorophenyl)methyl][(3*S*)-pyrrolidin-3-yl]amino}-2-methylpropan-2-ol *L*-tartrate

a) 1,1-Dimethylethyl (3*S*)-3-({[2-chloro-6-fluoro-phenylphenyl]methyl}amino)pyrrolidine-1-carboxylate

To 1,1-dimethylethyl (3*S*)-3-aminopyrrolidine-1-carboxylate (1.06g, 5.8mmol) and 2-chloro-6-fluoro-benzaldehyde (0.95g, 5.9mmol) in dichloroethane (10mL) was added sodium triacetoxyborohydride (3.69g, 17.4mmol) in DMF (2mL). The mixture was left to stir for 3 days at room temperature. To the reaction mixture was added water. After stirring for 10 mins, the chlorinated layer was isolated and purified by flash chromatography on silica, eluting with ethyl acetate/isohexane (20:80 to 40:60), to give the title compound as an oil.

MS: [M+H] = 329.

b) 1,1-Dimethylethyl (3*S*)-3-{[(2-chloro-6-fluoro-phenyl)methyl][2-(methoxy)-2-oxoethyl]amino}pyrrolidine-1-carboxylate

To a solution of 1,1-dimethylethyl (3*S*)-3-({[2-chloro-6-fluorophenyl]methyl}amino)pyrrolidine-1-carboxylate (0.30g, 0.81mmol) in acetonitrile, under nitrogen and at room temperature, was added methyl bromoacetate (0.09mL, 0.97mmol), sodium hydrogen carbonate (0.34g, 4.05mmole) and potassium iodide (0.07g, 0.40mmol). This was left to stir overnight at room temperature. Additional acetonitrile (2mL) and methyl bromoacetate (0.09mL, 0.97mmole) were added, and the reaction mixture heated to 60°C. After 2 h further methyl bromoacetate (0.97mL, 0.97mmol) was added. After 2.5 h further methyl bromoacetate (1.84mL, 1.94mmol) was added and the temperature increased to 80°C. After 2 hours the reaction mixture was allowed to cool, filtered and purified by flash chromatography on silica, eluting with ethyl acetate/isohexane (0:100 to 30:70), to give the title compound as an oil.

MS: [M+H] = 443.

c) 1,1-Dimethylethyl (3S)-3-[[(2-chloro-6-fluorophenyl)-methyl]((2-hydroxy-2-methypropyl)amino]pyrrolidine-1-carboxylate

To a solution of 1,1-dimethylethyl (3*S*)-3-{[(2-chloro-6-fluorophenyl)methyl][2-(methoxy)-2-oxoethyl]amino}-pyrrolidine-1-carboxylate (0.24g, 0.60mmol) in dry THF (2mL), under nitrogen and at -10°C, was added a solution of methyl magnesium bromide in toluene/THF (1.4M solution, 4.28mL, 5.99mmol) dropwise over 2 mins. After 3 hours water (50mL) was added to the reaction mixture followed by ammonium chloride (0.3g). The resulting mixture was extracted with diethyl ether (3x50mL). The combined ethereal extracts were washed with brine (50mL), then dried over sodium sulphate. Concentration *in vacuo* yielded a pale yellow oil.

MS: [M+H] = 401.

d) 1-{[(2-Chloro-6-fluorophenyl)methyl][(3*S*)-pyrrolidin-3-yl]amino}-2-methylpropan-2-ol *L*-tartrate

1,1-Dimethylethyl (3S)-3-[[(2-chloro-6-fluorophenyl)-methyl]((2-hydroxy-2-methypropyl)amino]pyrrolidine-1-carboxylate (0.23mg, 0.57mmol), trifluoroacetic acid (0.43mL, 5.74mmol) and dichloromethane (5mL) were stirred at room temperature for 3.5 h. The solution was evaporated *in vacuo* to give an oil. This was redissolved in methanol and filtered through a cationic ion exchange resin (Isolute ™ SCX-2). The basic components were isolated by elution with 2N ammonia in methanol. The eluate was evaporated *in vacuo* and the resultant oil converted to the L-tartrate acid salt (crystallisation from methanol/ethyl acetate/diethyl ether), to give the title compound as a white solid.

^{1}H NMR (300MHz, CD_3OD): δ_H 7.40-7.29 (m, 2H), 7.17-7.11 (t, 1H), 4.44 (s, 2H), 4.04-3.3.93 (m, 3H), 3.53-3.22 (m, 4H), 2.67-2.52 (q, 2H), 2.25-2.17 (m, 2H), 1.01 (s, 3H), 0.94 (s, 3H); MS: [M+H] = 301.

The following Examples were similarly prepared as described above for Example 166:

Example 167

1-{[(2-Phenyl-5-fluorophenyl)methyl][(3*S*)-pyrrolidin-3-yl]amino}-2-methylpropan-2-ol *L*-tartrate

^{1}H NMR (300MHz, CD_3OD): δ_H 7.61-7.58 (d, 1H), 7.50-7.39 (m, 3H), 7.31-7.22 (m, 3H), 7.10-7.05 (t, 1H), 4.44 (s, 2H), 3.90-3.76 (m, 2H), 3.68-3.60 (m, 1H), 3.35-3.30 (m, 1H), 3.20-3.05 (m, 2H), 3.00-2.92 (m, 1H), 2.53-2.43 (m, 2H), 1.90-1.68 (m, 2H), 1.19-1.18 (m, 6H); MS: [M+H] = 343.

Example 168

1-{{[2-(Trifluoromethyl)phenyl]methyl}[(3*S*)-pyrrolidin-3-yl]amino}-2-methylpropan-2-ol *L*-tartrate

MS: [M+H] = 317.

Example 169

N-(2-Methylpropyl)-*N*-(4-methylbenzyl)-pyrrolidin-3-amine

a) To a suspension of 4-nitrophenyl carbonate resin (1.56g, 1.5mmol) in DMF (15mL) was added 3-trifluoro-acetamidopyrrolidine hydrochloride (0.98g, 4.5mmol) and *N,N*-diisopropylethylamine (1.56mL, 9mmol). The mixture was agitated gently for 3 hours, then filtered and washed with DMF (2 x 50mL), methanol (3 x 50mL) and THF (4 x 50mL).

b) To a suspension of the resin prepared in step (a) in THF (27mL) was added a solution of lithium hydroxide hydrate (315mg, 7.5mmol) in water (3mL). The mixture was

agitated gently for 22 hours, then filtered, washed with THF (40mL), THF/water (1:1 v/v, 40mL), THF (3 x 40mL) and methanol (4 x 40mL), and dried *in vacuo* at 40°C.

c) Aliquots (47mg, 0.05mmol) of the resin prepared in step (b) were dispensed into a Titan 24-well Filter Plate (Radleys) fitted with 5 μm PTFE frits. The bottom of the filter plate was closed with a PTFE seal retained by a Combi-Clamp (Radleys). To each well was added a 0.5M solution of a substituted benzaldehyde in trimethylorthoformate (1.0 mL, 0.5mmol), exemplified here by 4-methylbenzaldehyde. The top of the plate was closed with a PTFE seal retained by the Combi-Clamp and the whole assembly agitated by orbital shaking for 66 hrs. After removal of the seals the reactions were filtered under a slight vacuum and washed with TMOF (3 x 2.5mL) and DMF (3 x 2.5mL).

d) The bottom of the filter plate was closed with a PTFE seal retained by a Combi-Clamp. To each well was added DMF/acetic acid (9:1 v/v, 0.5mL) and a 1.0M solution of sodium cyanoborohydride in DMF/acetic acid (9:1 v/v, 0.5mL, 0.5mmol). The top of the plate was closed with a PTFE seal retained by the Combi-Clamp and the whole assembly agitated by orbital shaking for 23 hrs. After removal of the seals the reactions were filtered under a slight vacuum and washed with DMF (4 x 2.5mL).

e) The bottom of the filter plate was closed with a PTFE seal retained by a Combi-Clamp. To each well was added DMF (0.5mL), a 1.0M solution of an aldehyde in DMF (0.5mL, 0.5mmol) (exemplified here by 2-methyl-propanaldehyde) and a 0.5M solution of sodium triacetoxyborohydride in DMF (0.5mL, 0.25mmol). The top of the plate was closed with a PTFE seal retained by the Combi-Clamp and the whole assembly agitated by orbital shaking for 23 hours. After removal of the seals the reactions were filtered under a slight vacuum and washed with DMF (2.5mL), ethanol (2 x 2.5mL) and DCM (4 x 2.5mL).

f) The bottom of the filter plate was closed with a PTFE seal retained by a Combi-Clamp. To each well was added a TFA/H_2O mixture (95:5 v/v, 1mL). The top of the plate was closed with a PTFE seal retained by the Combi-Clamp and the whole assembly

agitated by orbital shaking for 6 hours. After removal of the seals the reactions were filtered under a slight vacuum and washed with DCM (2 x 2mL). Appropriate filtrates and washings were combined and volatile components removed by vacuum evaporation. Each residue was dissolved in methanol (1mL) and the solutions applied to methanol-washed SCX-2 cation-exchange cartridges (0.5 g/2.5mL) (Jones Chromatography). After draining under gravity the cartridges were washed with methanol (2.5mL) and the products then eluted using a 2M solution of ammonia in methanol (2.5mL). Removal of volatile components by vacuum evaporation gave the desired products.

By this means was prepared *N*-(2-methylpropyl)-*N*-(4-methylbenzyl)-pyrrolidin-3-amine.

^{1}H NMR δ_H (300 MHz $CDCl_3$): 7.23-7.20 (2H, d), 7.11-7.09 (2H, d), 3.63-3.49 (2H, q), 3.36-3.25 (1H, m), 3.00-2.86 (2H, m), 2.84-2.72 (2H, m), 2.33 (3H, s), 2.22-2.20 (2H, d), 1.84-1.63 (3H, m), 0.88-0.85 (6H, dd); [M+H] = 247.

The following Examples were similarly prepared, as described above for Example 169, using the appropriate substituted benzaldehyde in step (c) and the appropriate aldehyde in step (e):

Example 170

N-(2-Methylpropyl)-*N*-(4-chlorobenzyl)-pyrrolidin-3-amine

MS: [M+H] = 267/269.

Example 171

N-(2-Methylpropyl)-*N*-(4-methoxybenzyl)-pyrrolidin-3-amine

MS: [M+H] = 263

Example 172

N-(2-Methylpropyl)-*N*-(3,4-dichlorobenzyl)-pyrrolidin-3-amine

MS: [M+H] = 301/303/305.

Example 173

N-(2-Methylpropyl)-*N*-(2-trifluoromethylbenzyl)-pyrrolidin-3-amine

MS: [M+H] = 301

Example 174

N-Cyclohexylmethyl-*N*-benzyl-pyrrolidin-3-amine

MS: [M+H] = 273

Example 175

N-Cyclohexylmethyl-*N*-(4-methoxybenzyl)-pyrrolidin-3-amine

MS: [M+H] = 303

Example 176

N-Cyclohexylmethyl-*N*-(4-methylbenzyl)-pyrrolidin-3-amine

MS: [M+H] = 287

Example 177

N-Cyclohexylmethyl-*N*-(3,4-dichlorobenzyl)-pyrrolidin-3-amine

MS: [M+H] = 341/343/345.

Example 178

N-Cyclopropylmethyl-*N*-(4-chlorobenzyl)-pyrrolidin-3-amine

MS: [M+H] = 265/267.

Example 179

N-Cyclopropylmethyl-*N*-(4-methoxybenzyl)-pyrrolidin-3-amine

MS: [M+H] = 261

Example 180

N-Cyclopropylmethyl-*N*-(3,4-dichlorobenzyl)-pyrrolidin-3-amine

MS: [M+H] = 299/301/303.

Example 181

N-Cyclopropylmethyl-*N*-(2-trifluoromethylbenzyl)-pyrrolidin-3-amine

MS: [M+H] = 299

Example 182

N-Butyl-*N*-benzyl-pyrrolidin-3-amine

MS: [M+H] = 233

Example 183

N-Butyl-*N*-(4-chlorobenzyl)-pyrrolidin-3-amine

MS: [M+H] = 267/269.

Example 184

N-Butyl-*N*-(4-methoxybenzyl)-pyrrolidin-3-amine

MS: [M+H] = 263

Example 185

N-Butyl-*N*-(4-methylbenzyl)-pyrrolidin-3-amine

MS: [M+H] = 247

Example 186

N-Butyl-*N*-(3,4-dichlorobenzyl)-pyrrolidin-3-amine

MS: [M+H] = 301/303/305.

Example 187

N-Butyl-*N*-(2-trifluoromethylbenzyl)-pyrrolidin-3-amine

MS: [M+H] = 301

Example 188

(3*S*)-*N*-[(3*R*)-Tetrahydrofuran-3-yl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}pyrrolidin-3-amine *L*-tartrate

a) (3*S*)-Tetrahydrofuran-3-yl 4-methylbenzenesulfonate

To a stirred solution of (3*S*)-tetrahydrofuran-3-ol (1.76g, 20mmol) dissolved in dry pyridine (20mL)was added 4-methylbenzenesulfonyl chloride (4.19g, 22mmol). The mixture was stiired at room temperature for 4 h, then was diluted with ethyl acetate and washed with aqueous citric acid. The organic extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate/cyclohexane (0:100 to 30:70), to yield the title compound as a white solid.

b) 1,1-Dimethylethyl (3*S*)-3-[(3*R*)-tetrahydrofuran-3-ylamino]pyrrolidine-1-carboxylate

A mixture of 1,1-dimethylethyl (3*S*)-3-amino-pyrrolidine-1-carboxylate (0.95g, 5.1mmol), (3*S*)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate (0.90g, 3.7mmol) and anhydrous potassium carbonate (0.53g, 3.8mmol) was stirred and heated at 100°C for 2 days. The reaction mixture was cooled and extracted from water into ethyl acetate. The organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica, eluting with methanol/ethyl acetate (0:100 to 30:70), to yield the title compound as an oil.

c) 1,1-Dimethylethyl (3*S*)-3-((3*R*)-tetrahydrofuran-3-yl{[2-(trifluoromethyl)phenyl]methyl}amino)pyrrolidine-1-carboxylate

A mixture of 1,1-dimethylethyl (3*S*)-3-[(3*R*)-tetrahydrofuran-3-ylamino]pyrrolidine-1-carboxylate (0.20g, 0.78mmol), 2-(trifluoromethyl)benzyl bromide (0.22g, 0.94mmol) and anhydrous potassium carbonate (0.16g, 1.17mmol) in acetonitrile was heated at reflux for 3 days. The reaction was extracted from water into ethyl acetate, and the combined organic extracts dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate/cyclohexane (20:80 to 40:60), to yield the title compound as an oil.

d) (3*S*)-*N*-[(3*R*)-Tetrahydrofuran-3-yl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}pyrrolidin-3-amine *L*-tartrate

To a stirred solution of 1,1-dimethylethyl (3*R*)-3-((3*R*)-tetrahydrofuran-3-yl{[2-(trifluoromethyl)phenyl]-methyl}amino)pyrrolidine-1-carboxylate (0.12g, 0.29mmol) in dichloromethane (4mL) was added trifluoroacetic acid (2mL). After stirring at room temperature for 3 h the solvent was removed *in vacuo* and the crude product taken up in methanol. This solution was absorbed onto a cationic ion exchange resin (Isolute ™ SCX-2) and the basic components recovered from the column by elution with 2N ammonia in methanol. The eluate was evaporated, taken up again in methanol and L-tartaric acid (1 equivalent) added. The solvent was removed *in vacuo* and the resultant gum triturated with diethyl ether to yield the title compound as a pink microcrystalline solid.

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.82 (d, 1H), 7.57 (d, 1H), 7.53 (t, 1H), 7.32 (t, 1H), 4.31 (s, 2H), 3.92-3.82 (m, 3H), 3.70-3.47 (m, 5H), 3.37-3.22 (m, 2H), 3.17-3.03 (m, 1H), 2.94 (dd, 1H), 2.12-1.96 (m, 2H), 1.85-1.67 (m, 2H); MS: [M+H] = 315.

Example 189

(3*S*)-*N*-[(3*S*)-Tetrahydrofuran-3-yl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}pyrrolidin-3-amine *L*-tartrate

Prepared as described above for Example 188, from (3*R*)-tetrahydrofuran-3-ol.

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.81 (d, 1H), 7.57 (d, 1H), 7.53 (t, 1H), 7.32 (t, 1H), 4.30 (s, 2H), 3.95-3.80 (m, 3H), 3.71-3.50 (m, 5H), 3.34-3.22 (m, 2H), 3.17-3.05 (m, 1H), 2.89 (dd, 1H), 2.14-1.95 (m, 2H), 1.89-1.73 (m, 2H); MS: [M+H] = 315.

The following Examples were prepared as described above for Examples 188 and 189, from the appropriate enantiomer of tetrahydrofuran-3-ol and the substituted benzyl bromide:

Example 190

(3*S*)-*N*-([1,1'-Biphenyl]-2-ylmethyl)-*N*-[(3*R*)-tetrahydrofuran-3-yl]pyrrolidin-3-amine *L*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.63 (d, 1H), 7.49-7.26 (m, 5H), 7.19 (dd, 1H), 4.44 (s, 2H), 3.95-3.85 (m, 1H), 3.70 (bs, 2H), 3.66-3.47 (m, 5H), 3.33-3.05 (m, 3H), 2.87 (dd, 1H), 2.06-1.86 (m, 2H), 1.82-1.62 (m, 2H); MS: [M+H] = 323.

Example 191

(3*S*)-*N*-([1,1'-Biphenyl]-2-ylmethyl)-*N*-[(3*S*)-tetrahydrofuran-3-yl]pyrrolidin-3-amine *L*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.62 (d, 1H), 7.50-7.23 (m, 5H), 7.19 (dd, 1H), 4.47 (s, 2H), 3.95-3.84 (m, 1H), 3.76 (d, 1H), 3.65 (d, 1H), 3.65-3.44 (m, 5H), 3.37-3.27 (m, 1H), 3.20-3.07 (m, 2H), 2.86-2.76 (m, 1H), 2.03-1.69 (m, 4H); MS: [M+H] = 323.

Example 192

(3*S*)-*N*-[(2-Chloro-6-fluorophenyl)methyl]-*N*-[(3*R*)-tetrahydrofuran-3-yl]pyrrolidin-3-amine *L*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.28-7.14 (m, 2H), 7.00 (m, 1H), 4.30 (s, 2H), 3.98-3.88 (m, 1H), 3.88-3.78 (m, 3H), 3.68 (m, 1H), 3.56-3.40 (m, 3H), 3.40-3.28 (m, 1H), 3.28-3.05 (m, 3H), 2.08-1.93 (m, 3H), 1.90-1.76 (m, 1H); MS: [M+H] = 299/301.

Example 193

(3*S*)-*N*-[(2-Chloro-6-fluorophenyl)methyl]-*N*-[(3*S*)-tetrahydrofuran-3-yl]pyrrolidin-3-amine *L*-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.39-7.25 (m, 2H), 7.11 (m, 1H), 4.42 (s, 2H), 4.10-3.98 (m, 1H), 3.94 (dd, 2H), 3.91-3.74 (m, 2H), 3.74-3.52 (m, 3H), 3.52-3.41 (m, 1H), 3.33-3.17 (m, 3H), 2.24-2.00 (m, 4H); MS: [M+H] = 299/301.

Example 194

(3*S*)-*N*-[(Tetrahydrofuran-3-yl)methyl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}pyrrolidin-3-amine *L*-tartrate

a) 1,1-Dimethylethyl (3*S*)-3-[(tetrahydrofuran-3-yl)methylamino]pyrrolidine-1-carboxylate

A mixture of 1,1-dimethylethyl (3*S*)-3-amino-pyrrolidine-1-carboxylate (1.86g, 10mmol), tetrahydrofuran-3-carboxaldehyde (2.0g, 10mmol) and anhydrous magnesium sulfate (5.0g) in dichloroethane (15mL) for 10 mins, then sodium triacetoxyborohydride (4.2g, 20mmol) was added in portions over 30 mins. The reaction mixture was left to stir for 3 days. The reaction mixture was diluted with water and extracted into dichloromethane. The organic extracts were washed with water, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica, eluting with methanol/chloroform (0:100 to 10:90), to yield the title compound as an oil.

b) 1,1-Dimethylethyl (3*S*)-3-{[(tetrahydrofuran-3-yl)methyl]{[2-(trifluoromethyl)phenyl]methyl}-amino}pyrrolidine-1-carboxylate

To a stirred solution of 1,1-dimethylethyl (3*S*)-3-[(tetrahydrofuran-3-yl)methylamino]pyrrolidine-1-carboxylate (0.54g, 2mmol) and 2-(trifluoromethyl)-benzaldehyde (0.52g, 3mmol) in dichloroethane (20mL) was added sodium triacetoxyborohydride (0.85g, 4mmol). The reaction mixture was stirred at room temperature for 18 h, then quenched by addition of 2M sodium hydroxide. After stirring for 30 mins, the mixture was extracted into ethyl acetate, and the combined organic extracts washed with brine, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate/cyclohexane (10:90 to 30:70), to yield the title compound as an oil.

c) (3*S*)-*N*-[(Tetrahydrofuran-3-yl)methyl]-*N*-{[2-(trifluoromethyl)phenyl]methyl}pyrrolidin-3-amine *L*-tartrate

1,1-Dimethylethyl (3*S*)-3-{[(tetrahydrofuran-3-yl)methyl]{[2-(trifluoromethyl)phenyl]methyl}-amino}pyrrolidine-1-carboxylate was deprotected and purified as described above in Example 192 d).

^{1}H NMR (300 MHz, CD_3OD) δ_H: 7.75 (dd, 1H), 7.58 (d, 1H), 7.53 (t, 1H), 7.33 (t, 1H), 4.30 (s, 2H), 3.81 (bt, 2H), 3.75-3.47 (m, 4H), 3.42 (dd, 1H), 3.35-3.21 (m, 2H), 3.16-3.03 (m, 1H), 3.04-2.92 (m, 1H), 2.55-2.40 (m, 2H), 2.36-2.20 (m, 1H), 2.09-1.80 (m, 1H), 1.90-1.76 (m, 2H), 1.57-1.42 (m, 1H); MS: [M+H] = 329.

Example 195

(3S)-*N*-(2-Methylpropyl)-*N*-{[3-phenylpyrid-2-yl]methyl}-pyrrolidin-3-amine, *L*-tartrate

a) (3-Phenylpyridin-2-yl)methanol

To 3-phenylpyridine-2-carboxylic methyl ester (2.00g, 9.38mmol) in THF, at 0°C under nitrogen, was added lithium borohydride (0.13g, 5.85mmol) in portions over 30 mins. The mixture was allowed to warm to room temperature and left to stir overnight. The mixture was quenched with 2N sodium hydroxide solution (10mL) and extracted with ethyl acetate (2 x 50mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give an oil. This was purified by flash chromatography on silica, eluting with ethyl acetate/isohexane (0:100 to 40:60), to give the title compound as an oil.

MS: [M+H] = 186.

b) 3-Phenylpyridine-2-carbaldehyde

To oxalyl chloride in dichloromethane (2M solution, 1.59mL, 2.97mmol) under nitrogen at -55°C was added DMSO (0.38mL, 5.40mmol) in dichloromethane (0.5mL), followed by (3-phenylpyridin-2-yl)methanol (0.50g, 2.70mmol) in dichloromethane (1.25mL). After 15 mins, triethylamine (1.88mL, 13.50mmol) was added. After a further 15 minutes, the mixture was allowed to warm to room temperature. On reaching room temperature, water (20mL) was added. This was extracted with dichloromethane (20mL). The dichloromethane was washed with water (20mL), brine (20mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as an oil.

MS: [M+H] = 184.

c) 1,1-Dimethylethyl (3*S*)-3-({[3-phenylpyrid-2-yl]methyl}amino)pyrrolidine-1-carboxylate

Sodium triacetoxyborohydride (0.37g, 1.76mmol) in DMF (1mL) was added to a stirred solution 1,1-dimethylethyl (3*S*)-3-aminopiperidine-1-carboxylate (0.25g, 1.47mmol) and 3-phenylpyridine-2-carbaldehyde (0.27g, 1.47mmol) in 1,2-dichloroethane (4mL). After stirring under nitrogen at room temperature for 1 day, the reaction mixture was diluted with methanol (6mL) and absorbed onto a cationic ion exchange resin (Isolute ™ SCX-2). After washing the cartridge with methanol (25mL),

the basic components were isolated by elution with 2N ammonia in methanol and the eluate evaporated to give an oil. This was purified by flash chromatography on silica, eluting with methanol/dichloromethane (0:100 to 30:70), to give the title compound as an oil.

MS: [M+H] = 354.

d) 1,1-Dimethylethyl (3*S*)-3-((2-methylpropyl){[3-phenylpyrid-2-yl]methyl}amino)pyrrolidine-1-carboxylate

Sodium triacetoxyborohydride (0.25g, 1.19mmol) in DMF (1mL) was added to a stirred solution of 1,1-dimethylethyl (3*S*)-3-({[3-phenylpyrid-2-yl]methyl}amino)-pyrrolidine-1-carboxylate (0.14g, 0.40mmol)and isobutyraldehyde (0.11mL, 1.19mmol) in 1,2-dichloroethane (4mL). After stirring under nitrogen at room temperature for 1 day, the reaction mixture was diluted with methanol (6mL) and absorbed onto a cationic ion exchange resin (Isolute ™ SCX-2). After washing the cartridge with methanol (25mL), the basic components were isolated by elution with 2N ammonia in methanol and the eluate evaporated to give an oil.

MS: [M+H] = 410.

e) (3S)-*N*-(2-Methylpropyl)-*N*-{[3-phenylpyrid-2-yl]methyl}pyrrolidin-3-amine, *L*-tartrate

1,1-Dimethylethyl (3*S*)-3-((2-methylpropyl){[3-phenylpyrid-2-yl]methyl}amino)pyrrolidine-1-carboxylate (0.136g, 0.335mmol), trifluoroacetic acid (1mL) and dichloromethane (4mL) were stirred at room temperature for 1 day. The solution was evaporated *in vacuo* to give an oil. This was redissolved in methanol and filtered through a cationic ion exchange resin (Isolute ™ SCX-2). The basic components were isolated by elution with 2N ammonia in methanol. The eluate was evaporated *in vacuo* and the resultant oil converted to the *L*-tartaric acid salt (triturated with diethyl ether), to give the title compound as a white solid.

^{1}H NMR (300MHz, CD_3OD): δ_H 8.58–8.56 (dd, 1H), 7.71-7.68 (dd, 1H), 7.53-7.38 (m, 6H), 4.43 (s, 2H), 3.87 (s, 2H), 3.56-3.47 (m, 1H), 3.38-3.30 (m, 1H), 3.24-3.12 (m, 2H), 2.99-2.93 (dd, 1H), 2.26-2.14 (m, 2H), 2.02-1.91 (m, 1H), 1.88-1.74 (m, 1H), 1.22-1.09 (m, 1H), 1.22-1.09 (m, 6H); MS: [M+H] = 310.

The following Example was similarly prepared, as described above for Example 195:

Example 196

(3S)-*N*-(Cyclohexyl)-*N*-{[2-(3-phenyl)pyridyl]methyl}-pyrrolidin-3-amine, *L*-tartrate

^{1}H NMR (300MHz, CD_3OD): δ_H 8.62–8.60 (dd, 1H), 7.73-7.70 (dd, 1H), 7.57-7.38 (m, 6H), 4.43 (s, 2H), 4.01-3.88 (m, 2H), 3.78-3.69 (m, 1H), 3.41-3.33 (m, 1H), 3.28-3.19 (m, 1H), 3.14-3.00 (m, 2H), 2.49-2.41 (m, 1H), 2.04-1.86 (m, 2H), 1.72-1.54 (m, 4H), 1.44-1.40 (m, 1H), 1.15-0.87 (m, 5H); MS: [M+H] = 336.

Example 197

(3S)-*N*-(2-Methylpropyl)-*N*-{[2-(3-pyridyl)-phenyl]methyl}pyrrolidin-3-amine, *L*-tartrate

a) 1,1-Dimethylethyl (3*S*)-3-(2-methylpropyl amino)-pyrrolidine-1-carboxylate

1,1-Dimethylethyl (3*S*)-3-aminopyrrolidine-1-carboxylate (2.00g, 11.6mmol), isobutyraldehyde (1.07mLg, 11.6mmol), 10% palladium on carbon (0.23g) and methanol (120mL) were hydrogenated at 60psi for 2 h using a Parr hydrogenator. The catalyst was filtered off and the filtrate evaporated *in vacuo* to give the title compound as an off-white solid.

MS: [M+H] = 243.

b) 2-(3-Pyridyl)benzaldehyde

To $Pd(PPh_3)_4$ (0.085g, 0.07mmol) in acetonitrile (6mL), under nitrogen, was added water (2mL) followed by 2-formylphenylboronic acid (0.55g, 3.68mmol), 3-bromopyridine (0.36 mL, 3.68mmol) and potassium carbonate (2.69g, 22.07mmol). After stirring for 3 days at 60°C, the reaction mixture was purified by flash chromatography on silica, eluting with ethyl acetate/isohexane (10:90 to 30:70), to give the title compound as an oil.

MS: [M+H] = 184.

c) 1,1-Dimethylethyl (3*S*)-3-((2-methylpropyl){[2-(3-pyridyl)phenyl]methyl}amino)pyrrolidine-1-carboxylate

Sodium triacetoxyborohydride (0.35g, 1.64mmol) in DMF (1mL) was added to a stirred solution of 1,1-dimethylethyl (3*S*)-3-(2-methylpropylamino)pyrrolidine-1-carboxylate and 2-(3-pyridyl)benzaldehyde (0.265g, 1.09mmol)in 1,2-dichloroethane (4mL). After stirring under nitrogen at room temperature for 1 day, the reaction mixture was purified by flash chromatography on silica, eluting with ethyl acetate/isohexane (0:100 to 40:60), to give the title compound as an oil.

MS: [M+H] = 410.

d) (3S)-*N*-(2-Methylpropyl)-*N*-{[2-(3-pyridyl)-phenyl]methyl}pyrrolidin-3-amine, *L*-tartrate

1,1-Dimethylethyl (3S)-3-((2-methylpropyl){[2-(pyridylmethyl)phenyl]methyl}amino)pyrrolidine-1-carboxylate (0.139mg, 0.335mmol), trifluoroacetic acid (4mL) and dichloromethane (10mL) were stirred at room temperature for 1 day. The solution was evaporated *in vacuo* to give an oil. This was redissolved in methanol and filtered through a cationic ion exchange resin (Isolute ™ SCX-2). The basic components were isolated by elution with 2N ammonia in methanol. The eluate was

evaporated *in vacuo* and the resultant oil converted to the *L*-tartaric acid salt (crystallisation from ethanol/ether), to give the title compound as a white solid.

^{1}H NMR (300MHz, CD_3OD): δ_H 8.58 (m, 2H), 7.90-7.87 (m, 1H), 7.66-7.55 (m, 2H), 7.49-7.39 (m, 2H), 7.29-7.26 (m, 1H), 4.44 (s, 2H), 3.75-3.58 (m, 2H), 3.55-3.44 (m, 1H), 3.38-3.30 (m, 1H), 3.21-3.10 (m, 2H), 2.89-2.82 (dd, 1H), 2.21-2.19 (d, 2H), 1.94-1.69 (m, 2H), 1.54-1.41 (m, 1H), 0.80-0.75 (m, 6H); MS: [M+H] = 310.

Example 198

(3*S*)-*N*-(2-Methylpropyl)-*N*-{[2-(1-pyrazolyl)phenyl]-methyl}pyrrolidine-3-amine, *L*-tartrate

a) 1,1-Dimethylethyl (3*S*)-3-((2-methylpropyl){[2-(1-pyrazolyl)phenyl]methyl}amino)pyrrolidine-1-carboxylate

To copper iodide (1.4mg, 0.007mmol), potassium carbonate (0.098g, 0.802mmol) and pyrazole (0.099g, 1.46mmol), under nitrogen in DMF (1.5mL), was added (3S)-3-(2-methylpropyl){[(2-bromophenyl)methyl]amino}-pyrrolidine-1-carboxylate (0.300g, 0.729mmol). The reaction mixture was sealed in a 10mL microwave tube and heated in a microwave oven (100 watt power) to 160°C for 10 minutes, then at 170°C for 10 minutes, then finally at 200°C (150 watt power) for 10 minutes. To the reaction mixture was added water (5mL). This was extracted with dichloromethane (3 x 2mL). The combined extracts were purified by flash chromatography on silica, eluting with ethyl acetate/isohexane (0:100 to 40:60), to give the title compound as an oil.

MS: [M+H] = 399.

b) (3*S*)-*N*-(2-Methylpropyl)-*N*-{[2-(1-pyrazolyl)phenyl]-methyl}pyrrolidine-3-amine, *L*-tartrate

1,1-Dimethylethyl (3*S*)-3-((2-methylpropyl){[2-(1-pyrazolyl)phenyl]methyl}amino)pyrrolidine-1-carboxylate was deprotected as described above in Example 197 d).

^{1}H NMR (300MHz, CD_3OD): δ_H 7.91-7.90 (d, 1H), 7.79-7.75 (m, 2H), 7.57-7.43 (dd, 1H), 6.59-6.57 (m, 1H), 4.43 (s, 2H), 3.69-3.48 (m, 3H), 3.40-3.32 (m, 1H), 3.27-3.12 (m, 2H), 2.96-2.89 (dd, 1H), 2.25-2.23 (d, 2H), 2.02-1.92 (m, 1H), 1.88-1.74 (m, 1H), 1.70-1.57 (m, 1H), 0.90-0.87 (m, 6H); MS: [M+H] = 299.

Example 199

(3S)-*N*-Propyl-*N*-{[2-(trifluoromethyl)phenyl]methyl}-pyrrolidine-3-amine, *L*-tartrate

a) 1,1-Dimethyl (3S)-3-((pyridin-3-ylmethyl){[2-(trifluoromethyl)phenyl]methyl}amino)pyrrolidine-1-carboxylate

Sodium triacetoxyborohydride (22.55g, 106.4mmol) was added to a stirred solution of 1,1-dimethyl (3S)-3-({[2-(trifluoromethyl)phenyl]methyl}amino)pyrrolidine-1-carboxylate (36.66g, 106.4mmol), propionaldehyde (7.74mL, 106.4mmol) and 1,2-dichloroethane (180mL). After stirring under nitrogen at room temperature for 1 hour, the reaction mixture was diluted with dichloromethane (10mL) and washed with 2N sodium hydroxide, then with water. The organic phases were combined and the solvent removed *in vacuo*. The resultant oil was purified by flash chromatography on silica, eluting with ethyl acetate/cyclohexane (10:90 to 40:60), to give the title compound as an oil.

MS: [M+H] = 387.

b) (3S)-*N*-Propyl-*N*-{[2-(trifluoromethyl)phenyl]methyl}-pyrrolidine-3-amine, *L*-tartrate

1,1-Dimethyl (3S)-3 –(propyl{[2-(trifluoromethyl)-phenyl]methyl}amino)pyrrolidine-1-carboxylate (23.1g, 59.8mmol), TFA (45mL) and DCM (150mL) were stirred at room temperature for 1 day. The solution was evaporated *in vacuo* to give an oil. This was redissolved in methanol and filtered through a cationic ion exchange resin (Isolute ™ SCX-2). The basic components were isolated by elution with 2N ammonia in methanol. The eluate was evaporated *in vacuo* and the resultant oil converted to the L-tartaric acid salt to give, after recrystallisation from hot isopropanol, the title compound as a white solid.

^{1}H NMR (300MHz, CD_3OD): δ_H 7.97-7.92(d, 1H), 7.68-7.59 (m, 2H), 7.44-7.42(t, 1H), 4.41 (s, 2H), 3.96-3.82 (AB, 2H), 3.69-3.59 (m, 1H), 3.45-3.3.37 (m, 2H), 3.29-3.2 (m, 1H), 3.15-3.08 (m, 1H), 2.59-2.54 (m, 2H), 2.18-2.09 (m, 1H), 2.03-1.89 (m, 1H), 1.55-1.43 (m, 2H), 0.90-0.85 (t, 3H); MS: [M+H] = 287.

The following Examples were similarly prepared as described above for Example 199, by reductive alkylation of the appropriate pyrrolidine carboxylate with the appropriate aldehyde and subsequent deprotection:

Example 200

(3S)-N-{5-fluoro-2-(trifluoromethyl)phenyl]methyl}-N-propylpyrrolidin-3-amine D-tartrate

^{1}H NMR (300 MHz, CD_3OD) δ_H: 0.91 (t, 3H), 1.45-1.58 (m, 2H), 1.90-2.03 (m, 1H), 2.13-2.23 (m, 1H), 2.57-2.62 (m, 2H), 3.10-3.17 (m, 1H), 3.22-3.30 (m, 1H), 3.40-3.48 (m, 2H), 3.68 (quintet, 1H), 3.91 (q, 2H), 4.43 (s, 2H), 7.17 (t,d, 1H), 7.70-7.87 (m, 2H); MS: [M+H]= 305.

Example 201

(3S)-*N*-(Pyridin-3-ylmethyl)-*N*-{[2-(trifluoromethyl)-phenyl]methyl}pyrrolidin-3-amine, L-tartrate

^{1}H NMR (300MHz, CD_3OD): δ_H 8.41-8.40 (d, 1H), 8.29-8.27 (d, 1H), 7.76-7.74 (d, 2H), 7.54-7.48 (m, 2H), 7.28-7.24 (m, 2H), 4.30 (s, 2H), 3.79-3.76 (m, 2H), 3.71-3.60 (m, 2H), 3.58-3.52 (m, 1H), 3.36-3.22 (m, 2H), 3.14-3.07 (m, 2H), 2.11-1.92 (m, 2H); MS: [M+H] = 336.

Example 202

(3S)-*N*-[(4-Fluoro[1,1'-biphenyl]-2-methyl]-*N*-(pyridin-2-ylmethyl)pyrrolidin-3-amine, L-tartrate

^{1}H NMR (300MHz, CD_3OD): δ_H 8.35-8.32 (d, 1H), 7.65-7.51 (t, 1H), 7.48-7.00 (m, 9H), 6.91-6.76 (t, 1H), 4.31 (s, 2H), 3.67-3.44 (m, 4H), 3.41-3.20 (m, 1H), 3.18-2.92 (m, 4H), 1.89-1.69 (m, 2H); MS: [M+H] = 362.

Example 203

(3S)-*N*-[(4-Fluoro[1,1'-biphenyl]-2-methyl]-*N*-(pyridin-3-ylmethyl)pyrrolidin-3-amine, L-tartrate

^{1}H NMR (300MHz, CD_3OD): δ_H 8.28-8.26 (m, 2H), 7.59-7.56 (d, 1H), 7.36-7.05 (m, 8H), 6.93-6.87 (t, 1H), 4.32 (s, 2H), 3.62-3.50 (m, 4H), 3.45-3.34 (m, 1H), 3.27-3.01 (m, 3H), 2.98-2.83 (m, 1H), 1.97-1.73 (m, 2H); MS: [M+H] = 362.

Example 204

(3S)-*N*-[(2-Chloro-6-fluorophenyl)methyl]-*N*-(pyridin-2-ylmethyl)pyrrolidine-3-amine, L-Tartrate.

^{1}H NMR (300MHz, CD_3OD): δ_H 8.37-8.35 (d, 1H), 7.69-7.63 (t, 1H), 7.39-7.37 (d, 1H), 7.25-7.14 (m, 3H), 7.01-6.97 (t, 1H), 4.43 (s, 2H), 3.98-3.96 (m, 2H), 3.88-3.87 (m, 2H), 3.81-3.70 (m, 1H), 3.49-3.42 (m, 2H), 3.36-3.21 (m, 2H), 2.26-2.09 (m, 2H); MS: [M+H] = 320.

Example 205

(3S)-*N*-[(2-Chloro-6-fluorophenyl)methyl]-*N*-(pyridin-4-ylmethyl)pyrrolidine-3-amine, L-tartrate

^{1}H NMR (300MHz, CD_3OD): δ_H 8.30-8.29 (d, 1H), 8.20-8.18 (d, 1H), 7.61-7.59 (d, 1H), 7.18-7.03 (m, 3H), 6.91-6.84 (m, 1H), 4.33 (s, 2H), 3.82 (s, 2H), 3.76-3.61 (m, 3H), 3.40-3.32 (m, 2H), 3.19-3.11 (m, 2H), 2.16-2.04 (m, 2H); MS: [M+H] = 320.

Example 206

(3S)-*N*-[(2-Chloro-6-fluorophenyl)methyl]-*N*-(pyridin-3-ylmethyl)pyrrolidine-3-amine, L-tartrate

^{1}H NMR (300MHz, CD_3OD): δ_H 8.30-8.29 (d, 1H), 8.20-8.18 (d, 1H), 7.61-7.59 (d, 1H), 7.18-7.03 (m, 3H), 6.91-6.84 (m, 1H), 4.33 (s, 2H), 3.82 (s, 2H), 3.76-3.61 (m, 3H), 3.40-3.32 (m, 2H), 3.19-3.11 (m, 2H), 2.16-2.04 (m, 2H); MS: [M+H] = 320.

Example 207

(3S)-*N*-(Pyridin-2-ylmethyl)-*N*-{[2-(trifluoromethyl)-phenyl]methyl}pyrrolidin-3-amine, L-tartrate

MS: [M+H] = 336.

The compounds of the present invention are inhibitors of the uptake of one or more monoamines selected from serotonin, norepinephrine and dopamine. Their selectivity profiles may be determined using the assays described below (see also J. Gobel, D.L. Saussy and A. Goetz, J. Pharmacol. Toxicolo. (1999), 42, 237-244). Compounds of Formula I and their pharmaceutically acceptable salts exhibit a K_i value less than 100nM at one or more of these monoamines. Preferred compounds of Formula I and their pharmaceutically acceptable salts exhibit a K_i value less than 50nM at one or more of these monoamines. Especially preferred compounds of Formula I and their pharmaceutically acceptable salts exhibit a K_i value less than 20nM at one or more of these monoamines.

Biogenic amine transporters control the amount of neurotransmitters in the synaptic cleft. Inhibition of the respective transporter leads to a rise in that neurotransmitter. Inhibition of the individual transporters can be studied by a simple competitive binding assay using selective radioligands for the individual expressed human transporter site. Compounds may be compared for selectivity and potency on the human norepinephrine transporter (hNET), the h-serotonin transporter (hSERT) and the h-dopamine transporter (hDAT) using membranes prepared from HEK293 cells expressing the respective transporter site.

Norepinephrine Binding Assay

The ability of compounds to compete with [^{3}H]-Nisoxetine for its binding sites on cloned human norepinephrine membranes has been used as a measure of its ability to block norepinephrine uptake via its specific transporter.

Membrane Preparation

Cell pastes from large scale production of HEK-293 cells expressing cloned human noradrenaline transporters were homogenised in 4 volumes 50mM Tris.HCl containing 300mM NaCl and 5mM KCl, pH 7.4. The homogenate was centrifuged twice (40,000g,

10min, 4°C) with pellet re-suspension in 4 volumes Tris.HCl buffer after the first spin and 8 volumes after the second spin. The suspended homogenate was centrifuged (100g, 10min, 4°C) and the supernatant kept and re-centrifuged (40,000g, 20min, 4°C). The pellet was resuspended in Tris.HCl buffer containing the above reagents along with 10%w/v sucrose and 0.1mM PMSF. The membrane preparation was stored in aliquots (1ml) at -80°C until required. The protein concentration of the membrane preparation was determined using a BCA protein assay reagent kit.

[^{3}H]-Nisoxetine Binding Assay

Each well of a 96well microtitre plate was set up to contain the following:

50µl	2nM [N-methyl-^{3}H]-Nisoxetine hydrochloride (70-87Ci/mmol)
75µl	Assay buffer (50mM Tris.HCl pH 7.4 containing 300mM NaCl and 5mM KCl)
25µl	Test compound, assay buffer (total binding) or 10µM Desipramine HCl (non-specific binding)
50µl	WGA PVT SPA Beads (10mg/ml)
50µl	Membrane (0.2mg protein per ml.)

The microtitre plates were incubated at room temperature for 10 hours prior to reading in a Trilux scintillation counter. The results were analysed using an automatic spline fitting programme (Multicalc, Packard, Milton Keynes, UK) to provide Ki values for each of the test compounds.

Serotonin Binding Assay

The ability to compete with [^{3}H]-citalopram from its binding sites on cloned human serotonin membranes has been used as a measure of its ability to block serotonin uptake via its specific transporter (Ramamoorthy, S., Giovanetti, E., Qian, Y., Blakely, R., (1998) J. Biol. Chem. 273,2458).

Membrane Preparation.

The preparation of membrane is essentially similar to that for the norepinephrine membrane. The membrane preparation was stored in aliquots (1ml) at -70°C until required. The protein concentration of the membrane preparation was determined using BCA protein assay reagent kit.

[^{3}H]-Citalopram Binding Assay

Each well of a 96well microtitre plate was set up to contain the following:

50µl	2nM [^{3}H]-Citalopram (60-86Ci/mmol)
75µl	Assay buffer (50mM Tris.HCl pH 7.4 containing 150mM NaCl and 5mM KCl)
25µl	Diluted compound, assay buffer (total binding) or 100µM Fluoxetine (non-specific binding)
50µl	WGA PVT SPA Beads (40mg/ml)
50µl	Membrane preparation (0.4mg protein per ml)

The microtitre plates were incubated at room temperature for 10 hours prior to reading in a Trilux scintillation counter. The results were analysed using an automatic spline fitting programme (Multicalc, Packard, Milton Keynes, UK) to provide Ki (nM) values for each of the unknown compounds.

Dopamine Binding Assay

The ability to compete with [^{3}H]-WIN35,428 for its binding sites on cloned human dopamine membranes has been used as a measure of its ability to block dopamine uptake via its specific transporter (Ramamoorthy et al 1998) .

Membrane Preparation.

Is essentially the same as for serotonin membranes

[^{3}H]-WIN35,428 Binding Assay

Each well of a 96well microtitre plate was set up to contain the following:

50µl	4nM [^{3}H]-WIN35,428428 (84-87Ci/mmol)
75µl	Assay buffer (50mM Tris.HCl pH 7.4 containing 150mM NaCl and 5mM KCl)
25µl	Diluted compound, assay buffer(total binding) or 100µM Nomifensine (non-specific binding)
50µl	WGA PVT SPA Beads (10mg/ml)
50µl	Membrane preparation (0.2mg protein per ml.)

The microtitre plates were incubated at room temperature for 120 minutes prior to reading in a Trilux scintillation counter. The results were analysed using an automatic spline fitting programme (Multicalc, Packard, Milton Keynes, UK) to provide Ki values for each of the unknown compounds.

CYP2D6 Assays

CYP2D6 is a mammalian enzyme which is commonly associated with the metabolism of pharmaceutical compounds. Stability versus this enzyme is desirable because it improves the half-life of a systemically administered drug substance. Compounds may be tested both as substrates and as inhibitors of this enzyme by means of the following assays.

CYP2D6 substrate assay

This assay determines the involvement of the CYP2D6 in the extent of metabolism of a compound (i.e. reverse of the metabolic stability). Preferred compounds of the present invention exhibit less than 75% metabolism via the CYP2D6 pathway.

This assay is performed in vitro with human liver microsomes (HLM). The extent of metabolism (after 30 minutes) is determined in HLM in the absence and in the presence of the specific CYP2D6 chemical inhibitor (Quinidine). The difference in the extent of metabolism in the absence and presence of the inhibitor explains the involvement of CYP2D6 in the metabolism of the compound. The incubation conditions are as follows:

COMPOUND CONCENTRATION	4 μmol/L
BUFFER	0.1 mol/L sodium phosphate pH 7.4
βNADPH	1 mmol/L
MICROSOMAL PROTEIN of HLM	0.5 mg/mL
SPECIFIC CYP2D6 CHEMICAL INHIBITOR	Quinidine at 0 (without) or 2 μmol/L (with) the specific inhibitor
ORGANIC SOLVENT	0.25% acetonitrile
TIME/TEMPERATURE	0 and 30 minutes/37°C
REACTION VOLUME	100 μL

The compound is monitored by LC-MS.

CYP2D6 inhibition assay

This assay determines the inhibitor effect of a compound on the metabolism of a CYP2D6 specific probe substrate (i.e. Bufuralol, a substrate that is metabolized to a well-known metabolite and whose the metabolism is performed by the CYP2D6). Preferred compounds of the present invention exhibit an IC_{50} greater than 6μM as inhibitors of CYP2D6.

Bufuralol 1-hydroxylase activity is determined by using 0.5 mg/ml human liver microsomal protein (human biologics), 10 μmol/L bufuralol, in 0.1 M sodium phosphate buffer pH 7.4, incubated for 5 min at 37°C in the presence of 2 mM βNADPH, with 0, 5 or 25 μM of the test compound (inhibitor). The compound was dissolved in acetonitrile, such that the final concentration of acetonitrile in the incubation was 0.5%. The total reaction volume was 100 μl. The reaction was terminated by addition of 75 μl of methanol followed by centrifugation. 40 μl of the supernatant was analysed by HPLC.

A Beckman Ultrasphere C_{18} column (5 μm, 250 x 4.6 mm) was used, with a 13 minute gradient from 100% of solvent A (0.02 M potassium dihydrogen phosphate buffer pH 3/methanol (65/35)) to 100 % of solvent B (0.02 M potassium dihydrogen phosphate

buffer pH 3/methanol (20/80)), according to the following gradient. The run time was 20 minutes. Formation of 1'-hydroxybufuralol was detected by fluorimetric detection with extinction at λ 252 nm and emission at λ 302 nm.

Time (min)	Solvent A (%)	Solvent B (%)
0	100	0
8	0	100
12	0	100
13	100	0

The percent of inhibition is calculated as follows:

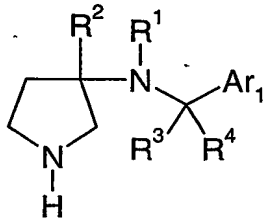
$$100 - \frac{100 \times \text{1'-hydroxybufuralol area formed with inhibitor}}{\text{1'-hydroxybufuralol area formed without inhibitor}}$$

The IC_{50} is calculated from the percent inhibition as follows (assuming competitive inhibition): $\frac{\text{Compound Concentration} \times (100 - \text{Percent of inhibition})}{\text{Percent of inhibition}}$

The IC_{50} estimation is assumed valid if inhibition is between 20% and 80%.

CLAIMS:

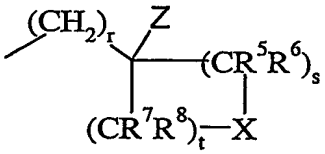
1. A compound of formula (I):



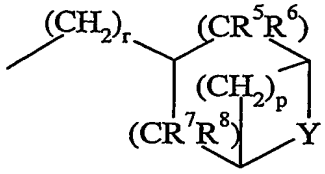
(I)

wherein

R^1 is C_1-C_6 alkyl (optionally substituted with 1, 2 or 3 halo substituents and/or with 1 substituent selected from -S-(C_1-C_3 alkyl), -O-(C_1-C_3 alkyl) (optionally substituted with 1, 2 or 3 F atoms), -O-(C_3-C_6 cycloalkyl), -SO_2-(C_1-C_3 alkyl), -CN, -COO-(C_1-C_2 alkyl) and –OH); C_2-C_6 alkenyl; -$(CH_2)_q$-Ar_2; or a group of formula (i) or (ii)



(i)



(ii)

R^2, R^3 and R^4 are each independently selected from hydrogen or C_1-C_2 alkyl;

R^5, R^6, R^7 and R^8 are at each occurrence independently selected from hydrogen or C_1-C_2 alkyl;

-X- is a bond, -CH_2-, -CH=CH-, -O-, -S-, or -SO_2-;

-Y- is a bond, -CH_2- or -O-;

-Z is hydrogen, –OH or -O-(C_1-C_3 alkyl);

p is 0, 1 or 2;

q is 0, 1 or 2;

r is 0 or 1;

s is 0, 1, 2 or 3;

t is 0, 1, 2, 3 or 4;

Ar_1 is phenyl, pyridyl, thiazolyl, benzothiophenyl or naphthyl; wherein said phenyl, pyridyl or thiazolyl group may be substituted with 1, 2 or 3 substituents each independently selected from halo, cyano, C_1-C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1-C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms) and -S-(C_1-C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms) and/or with 1 substituent selected from pyridyl, pyrazole, phenyl (optionally substituted with 1, 2 or 3 halo substituents) and phenoxy (optionally substituted with 1, 2 or 3 halo substituents); and wherein said benzothiophenyl or naphthyl group may be optionally substituted with 1, 2 or 3 substituents each independently selected from halo, cyano, C_1-C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms), -O-(C_1-C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms), and -S-(C_1-C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms);

Ar_2 is naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl, wherein said naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl may be substituted with 1, 2 or 3 substituents each independently selected from halo, C_1-C_4 alkyl (optionally substituted with 1, 2 or 3 F atoms) and -O-(C_1-C_4 alkyl) (optionally substituted with 1, 2 or 3 F atoms); and pharmaceutically acceptable salts thereof; provided that

(a) the cyclic portion of the group of formula (i) must contain at least three carbon atoms and not more than seven ring atoms;

(b) when –X- is –CH=CH-, then the cyclic portion of the group of formula (i) must contain at least five carbon atoms; and

(c) when –Z is –OH or -O-(C_1-C_3 alkyl), then –X- is -CH_2-;

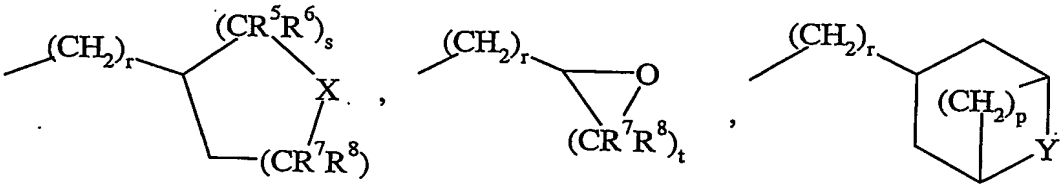
(d) when –Y- is –O- then p cannot be 0; and

(e) the compound 3-[(phenylmethyl)-(3S)-3-pyrrolidinylamino]-propanenitrile is excluded.

2. A compound according to claim 1 wherein

R^1 is C_1-C_6 alkyl, C_2-C_6 alkenyl, -$(CH_2)_m$-CF_3, -$(CH_2)_n$-S-(C_1-C_3 alkyl), -CH_2-COO-(C_1-C_2 alkyl), -(C_1-C_5 alkylene)-O-(C_1-C_3 alkyl), -(C_1-C_5 alkylene)-O-(C_3-

R^1 is C_1-C_6 alkyl, C_2-C_6 alkenyl, -$(CH_2)_m$-CF_3, -$(CH_2)_n$-S-(C_1-C_3 alkyl), -CH_2-COO-(C_1-C_2 alkyl), -(C_1-C_5 alkylene)-O-(C_1-C_3 alkyl), -(C_1-C_5 alkylene)-O-(C_3-C_6 cycloalkyl), -(C_1-C_5 alkylene)-SO_2-(C_1-C_3 alkyl), -(C_1-C_5 alkylene)-OCF_3, -(C_1-C_6 alkylene)-OH, -(C_1-C_5 alkylene)-CN, -$(CH_2)_q$-Ar_2 or a group of formula (ia), (ib) or (ii)



(ia) (ib) (ii)

R^2, R^3, R^4, R^5, R^6, R^7, R^8, -X-, -Y-, p, q, r and s are as defined in claim 1;

m is 1, 2 or 3;

n is 1, 2 or 3;

t is 2, 3 or 4;

-Ar_1 is phenyl, pyridyl, thiazolyl or naphthyl; wherein said phenyl, pyridyl or thiazolyl group may be substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl, cyano, C_1-C_4 alkyl, -O-(C_1-C_4 alkyl), -O-(C_1-C_4 difluoroalkyl), -O-(C_1-C_4 trifluoroalkyl), -S-(C_1-C_4 alkyl), -S-(C_1-C_2 trifluoroalkyl) and/or with 1 substituent selected from pyridyl, pyrazole, phenyl (optionally substituted with 1, 2 or 3 halo substituents) and phenoxy (optionally substituted with 1, 2 or 3 halo substituents); and wherein said naphthyl group may be optionally substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl, cyano, C_1-C_4 alkyl, -O-(C_1-C_4 alkyl), -O-(C_1-C_4 difluoroalkyl), -O-(C_1-C_4 trifluoroalkyl), -S-(C_1-C_4 alkyl), -S-(C_1-C_2 trifluoroalkyl);

Ar_2 is naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl, wherein said naphthyl, pyridyl, thiazolyl, furyl, thiophenyl, benzothiophenyl, or phenyl may be substituted with 1, 2 or 3 substituents each independently selected from halo, C_1-C_4 alkyl, trifluoromethyl and -O-(C_1-C_4 alkyl);

3. A compound according to claim 1 or claim 2 wherein R^2 is hydrogen.

4. A compound according to any one of claims 1 to 3 wherein R^3 and R^4 are hydrogen.

5. A compound according to any one of claims 1 to 4 wherein each R^5 and R^6 is hydrogen.

6. A compound according to any one of claims 1 to 5 wherein each R^7 and R^8 is hydrogen.

7. A compound according to any one of claims 1 to 6 wherein R^1 is C_1-C_6 alkyl.

8. A compound according to any one of claims 1 to 6 wherein R^1 is -(C_4-C_5 alkylene)-OH.

9. A compound according to any one of claims 1 to 6 wherein R^1 is a group of formula (i), r is 0, s is 2, t is 2, –Z is hydrogen and -X- is -O-, –S- or –SO_2-.

10. A compound according to any one of claims 1 to 6 wherein R^1 is a group of formula (i), r is 0, s is 1, 2 or 3, t is 1, –Z is hydrogen and -X- is –CH_2-.

11. A compound according to any one of claims 1 to 6 wherein R^1 is a group of formula (i), r is 1, s is 0, 1, 2 or 3, t is 1, –Z is hydrogen and -X- is –CH_2-.

12. A compound according to any one of claims 2 to 6 wherein R^1 is a group of the formula (ib), r is 1, t is 3, and each $R^7$and R^8 is hydrogen.

13. A compound according to any one of claims 1 to 6 wherein R^1 is -$(CH_2)_q$-Ar_2, and q is 1.

14. A compound according to claim 13 wherein -Ar_2 is pyridyl, phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl or C_1-C_4 alkyl.

15. A compound according to any one of claims 1 to 14 wherein -Ar_1 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl and C_1-C_4 alkyl and/or with 1 substituent selected from phenyl, phenyl substituted with 1, 2 or 3 halo substituents, pyridyl, pyrazole, phenoxy and phenoxy substituted with 1, 2 or 3 halo substituents; pyridyl; or pyridyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl and C_1-C_4 alkyl and/or with 1 substituent selected from phenyl and phenyl substituted with 1, 2 or 3 halo substituents.

16. A compound according to any one of claims 1 to 15 wherein –Ar_1 is phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl and C_1-C_4 alkyl and/or with 1 substituent selected from phenyl, phenyl substituted with 1, 2 or 3 halo substituents, pyridyl, pyrazole, phenoxy and phenoxy substituted with 1, 2 or 3 halo substituents.

17. A compound according to any one of claims 1 to 15 wherein –Ar_1 is phenyl substituted with 1 or 2 substituents each independently selected from halo, trifluoromethyl and C_1-C_4 alkyl and/or with 1 substituent selected from phenyl, phenyl substituted with 1, 2 or 3 halo substituents, pyridyl, pyrazole, phenoxy and phenoxy substituted with 1, 2 or 3 halo substituents.

18. A compound according to any one of claims 1 to 15 wherein –Ar_1 is pyridyl or pyridyl substituted with 1, 2 or 3 substituents each independently selected from halo, trifluoromethyl and C_1-C_4 alkyl and/or with 1 substituent selected from phenyl and phenyl substituted with 1, 2 or 3 halo substituents.

19. A compound according to any one of claims 1 to 15 wherein –Ar_1 is pyridyl substituted with 1 or 2 substituents each independently selected from halo,

trifluoromethyl and C_1-C_4 alkyl and/or with 1 substituent selected from phenyl and phenyl substituted with 1, 2 or 3 halo substituents.

20. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 19 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

21. A compound as claimed in any one of claims 1 to 19 or a pharmaceutically acceptable salt thereof, for use in therapy.

22. Use of a compound as claimed in any one of claims 1 to 19 or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a disorder of the nervous system.

23. Use as claimed in claim 19 wherein the disorder of the nervous system is selected from the group consisting of adjustment disorders (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood), age-associated learning and mental disorders (including Alzheimer's disease), alcohol addiction, antinociceptive pain, anxiety, apathy, attention-deficit (or other cognitive) disorders due to general medical conditions, attention-deficit hyperactivity disorder (ADHD), autism, bipolar disorder, borderline personality disorder, brain trauma, cardiovascular disorders, chronic fatigue syndrome, chronic or acute stress, chron's disease, cognitive disorders including mild cognitive impairment (MCI), conduct disorder, cyclothymic disorder, dementia of ageing, dementia of the Alzheimers type (DAT), depression (including adolescent depression and minor depression), dyspepsia, disruptive behavior disorders, drug addiction including cocaine abuse, dysthymic disorder, eating disorders (including bulimia and anorexia nervosa), emesis, emotional dysregulation, epilepsy, fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS), functional bowel disorders, gastric motility

disorders, gastroesophageal reflux for functional bowel disorders, gastrointestinal disorders, generalized anxiety disorder (GAD), headache, hypertension, hypotensive states including orthostatic hypotension, iletis, impulsive control disorders, incontinence (i.e., stress incontinence, genuine stress incontinence, urge incontinence and mixed incontinence), inflammatory bowel disorders, inhalation disorders, insterstitial cystitis, intoxication disorders (alcohol addiction), irritable bowel syndrome, ischemic bowel disease, mania, memory loss, mutism, nicotine addiction, obesity (i.e., reducing the weight of obese or overweight patients), obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, pain (including chronic pain, inflammatory pain, neuropathic pain, non-neuropathic non-inflammatory pain, persistent pain, persistent pain of inflammatory and/or neuropathic origin, headache and migraine), panic disorders, Parkinsonism, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder (i.e., premenstrual syndrome and late luteal phase dysphoric disorder), psoriasis, psychoactive substance use disorders, psychotic disorders (including schizophrenia, schizoaffective and schizophreniform disorders), seasonal affective disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome (i.e., wherein a patient who fails to maintain a satisfactory response to SSRI therapy after an initial period of satisfactory response), senile dementia, sexual dysfunction (including premature ejaculation and erectile difficulty), sleep disorders (such as narcolepsy and enuresis), smoking cessation, social phobia (including social anxiety disorder), specific developmental disorders, substance abuse (including alcohol addiction, tobacco abuse, symptoms caused by withdrawal or partial withdrawal from the use of tobacco or nicotine and drug addiction including cocaine abuse), TIC disorders (e.g., Tourette's Disease), tobacco addiction, trichotilomania, ulcerative colitis, urethral syndrome, vascular dementia and cognitive impairment associated with schizophrenia (CIAS).

24. A method for inhibiting the uptake of one or more monoamines selected from serotonin, dopamine and norepinephrine in a mammal, comprising administering to a mammal in need of such inhibition an effective amount of a compound as claimed in any one of Claims 1 to 19 or a pharmaceutically acceptable salt

thereof.

25. A method for treating disorders associated with dysfunction of the uptake of one or more monoamines selected from serotonin, dopamine and norepinephrine in a mammal, comprising administering to a patient in need thereof an effective amount of a compound as claimed in any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof.